COMPOUNDS HAVING TGFβ INHIBITORY ACTIVITY AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

BACKGROUND OF THE INVENTION

[0001] Field of Invention

The present invention relates to compounds having TGFβ inhibitory activity. The present invention also relates to a pharmaceutical composition useful for the prevention or treatment of diseases for which TGFβ inhibition is effective therapeutically.

[0002] Background Art

TGFβ (transforming growth factor-β) is an important cytokine for living organisms, which regulates growth and differentiation of cells, and repair and regeneration of tissue after its disorder. Disruption of its signal is known to cause onset and progress of various diseases.

Regarding the relationship between TGFβ and diseases, the fibrosis of organs or tissues is well known. The fibrosis of an organ or a tissue arise from excessive accumulation of extracellular matrix proteins within the organ , as a defence mechanism against damage of the organ by some cause. The extracelluar matrix protein refers to a substance surrounding cells of the tissue. For example, fibrotic proteins such as collagen and elastin, glycoconjugates such as proteoglycan, and glycoproteins such as fibronectin and laminin are mentioned as major extracellular matrix proteins.

[0003] When the level of fibrosis of an organ is low, the organ can be recovered to a normal state without leaving any repair scar. On the other hand, when the level of disorder of the organ is large or when the disorder continues, the fibrosis causes damage to the innate function of the organ. Further, the damage causes new fibrosis to create a vicious cycle. Ultimately, this causes organ failure and, in the worst case, sometimes leads to death.

[0004] TGFβ is known to play an important role in the

accumulation of the extracellular matrix proteins.

For example, the administration of TGFβ to normal animals is known to cause fibrosis in various tissues (International Review of Experimental Pathology, 34B: 43-67, 1993). Further, rapid fibrosis of tissues is also observed in trans-genetic mice for TGFβ1 and normal animals with gene-transfer of a TGFβ1 gene, (Proc. Natl. Acad. Sci. USA, 92: 2572-2576, 1995; Laboratory Investigation, 74: 991-1003, 1995).

[0005] TGFβ is considered to be involved in the fibrosis of tissues via the following mechanism.

1) TGFβ highly increases the level of extracellular matrix proteins such as fibronectin in cells (Journal of Biological Chemistry, 262: 6443-6446, 1987), collagen (Proc. Natl. Acad. Sci. USA, 85 1105-1108, 1988), and proteoglycan (Journal of Biological Chemistry, 263: 3039-3045, 1988).

2) TGFβ reduces the expression of degradative enzymes for extracellular matrix proteins (Journal of Biological Chemistry, 263: 16999-17005, 1988) and, in addition, highly promotes the expression of an inhibitor against the degradative enzymes for extracellular matrix proteins (Cancer Research, 49: 2553-2553, 1989). Consequently, the degradation of the extracellular matrix proteins is suppressed.

3) Further, TGFβ increases the expression of integrin as a receptor for an extracellular matrix proteins and promotes the deposition of the matrix proteins on cells (Journal of Biological Chemistry, 263: 4586-4592, 1988).

4) Furthermore, TGFβ proliferates cells which produce extracellular matrix proteins (American Journal of Physiology, 264: F199-F205, 1993).

[0006] TGFβ is known to be mainly involved in the fibrosis of organs such as kidney, liver, lung, heart, bone marrow, and skin.

For example, in the analysis of expression of TGFβ1, an increase in expression of TGFβ1 is observed in diseases such as human acute renal diseases, chronic renal diseases, diabetic

nephropathy, renal allograft rejection, HIV nephropathy, hepatic fibrosis, cirrhosis, pulmonary fibrosis, scleroderma, and keloid (New Engl. J. Med., 331, 1286-1292, 1994), and the expression is known to correlate with the expression of extracellular matirix proteins.

[0007] Further, it has been shown that the administration of a soluble form of TGFβ type II receptor or an anti-TGFβ neutralizating antibody can inhibit fibrosis and pathology in pathologic animal models of renal disease, diabetic nephropathy, hepatic fibrosis, pulmonary fibrosis, and scleroderma (Nature, 346: 371-374, 1990; Journal of the British Thoracic Society, 54: 805-812, 1999; Journal of Immunology, 163: 5693-5699, 1999; Human Gene Therapy, 11: 33-42, 2000; Proc. Natl. Acad. Sci. USA., 97: 8015-20, 2000).

These facts show that the inhibition of TGFβ is useful for the prophylaxis and therapy for the diseases involving fibrosis including chronic renal diseases.

[0008] Further, TGFβ is also known to be involved in restenosis and arteriosclerosis.

In restenosis model animals, an increase in expression of TGFβ1 and its receptor is observed in a disordered blood vessel, which suggests that TGFβ1 may be involved in the formation of new intima after balloon angioplasty injury (Clinical and Experimental Pharmacology and Physiology 23: 193-200, 1996).

For arteriosclerosis, a high level of expression of TGFβ1 is observed in non-foam macrophage infiltrated in an affected region in which active matrix synthesis takes place(American Journal of Physiology 146: 1140-1149, 1995), which suggests that the non-foam macrophage participates in extracellular matrix protein synthesis within an arteriosclerosis region through TGFβ1.

Further, in a migration test using cells, TGFβ1 is also reported to be a potent stimulating factor for migration of smooth muscle cells causative of arteriosclerosis and vascular restenosis (Biochem Biophys Res Commun., 169: 725-729, 1990).

[0009] TGFβ1 is also involved in wound repair.

For example, an experiment using a neutralizing antibody against TGFβ1 demonstrates that the inhibition of TGFβ1 suppresses excessive scar formation after the injury and is useful for functional recovery. Specifically, it is also known that the administration of a neutralizing antibody against TGFβ1 or TGFβ2 to rats can suppress scar formation and further promotes dermal cell construction via the suppression of dermal fibronectin and collagen deposition and a reduction in the number of monocytes and macrophages (Journal of Cellular Science 108: 985-1002, 1995). In other tissues, the acceleration of cure by the administration of an anti-TGFβ-neutralizing antibody is observed in a rabbit corneal injury model and a rat gastric ulcer model (Cornea 16: 177-187, 1997; An international Journal of gastroenterology & Hepatology 39: 172-175, 1996).

[0010] Further, TGFβ1 is also involved in peritoneal adhesion.

For example, it is suggested that the inhibition of TGFβ is effective for suppressing peritoneal adhesion and subdermal fibrous adhesion after surgery (J. Surg. Res., 65: 135-138, 1996).

It is reported in a number of articles that the administration of an anti-TGFβ neutralizing antibody or a soluble form of TGFβ type II receptor into model animals for cancer is also effective for suppressing tumor growth and cancer metastasis (Journal of Clinical Investigation, 92: 2569-76, 1993; Clinical Cancer Research 7: 2931-2940, 2001; Cancer Res. 59: 2210-6, 1999; Journal of Clinical Investigation 109: 1551-1559, 2002; Journal of Clinical Investigation 109: 1607-1615, 2002).

[0011] Tumors is considered to acquire tumor growth potential and metastatic ability by inducing angiogenesis on host side and by lowering immunity of the host side, through TGFβ produced by the tumors themselve, on the basis of studies using an anti-TGFβ neutralizing antibody. Thus, the inhibition

of TGFβ is considered to be effective for suppressing cancer metastasis and cancer cell growth.

[0012] It is also reported that an anti-TGFβ1 neutralizing antibody is effective in ex vivo expansion of hematopoietic stem cells (Experimental Hematology 26: 374-381, 1998).

Further, TGFβ1 is known to have growth inhibitory activity against a number of other cell as well as against hematopoietic stem cells.

Accordingly, the inhibition of TGFβ is expected to be effective for ex vivo expansion of a number of cells including hematopoietic stem cells.

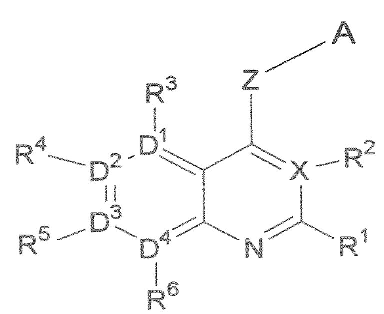
SUMMARY OF THE INVENTION

[0013] The present inventors have now found that a certain group of naphthyridine derivatives, quinoline derivatives, quinazoline derivatives, thienopyridine derivatives, and thienopyrimidine derivatives have inhibitory activity against TGFβ1. The present invention has been made based on such finding.

An object of the present invention is to provide compounds having potent TGFβ inhibitory activity.

[0014] In one embodiment of the present invention, there are provided compounds of formula (I) or pharmaceutically acceptable salts or solvates thereof:

[Chemical formula 1]

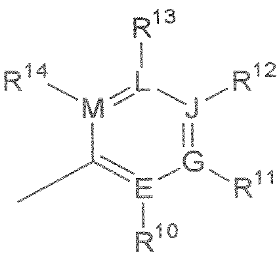


(I)

wherein

A represents a group of formula (a):

[Chemical formula 2]



(a)

Z represents -O-, -N(-R^Z)-, -S-, or -C(=O)- wherein R^Z represents a hydrogen atom or unsubstituted C1-4 alkyl,

D^1, D^2, D^3, D^4, X, E, G, J, L, and M, which may be the same or different, represent C or N,

R^1 to R^6 and R^{10} to R^{14}, which may be the same or different, represent

(1) a hydrogen atom;

(2) a halogen atom;

(3) hydroxyl;

(4) cyano group;

(5) nitro group;

(6) C1-6 alkyl;

(7) C2-6 alkenyl;

(8) C2-6 alkynyl;

(9) C1-6 alkoxy;

(10) C1-6 alkylthio;

wherein (6) C1-6 alkyl, (7) C2-6 alkenyl, (8) C2-6 alkynyl, (9) C1-6 alkoxy, and (10) C1-6 alkylthio are optionally substituted by

(I) hydroxyl,

(II) a halogen atom,

(III) C1-4 alkoxy,

(IV) an oxygen atom,

(V) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group wherein the carbocyclic or heterocyclic group is optionally substituted by C1-4 alkyl, C1-4 alkoxy, a halogen atom, or a five- or six-membered carbocyclic or heterocyclic group, and the C1-4 alkyl group is optionally substituted by hydroxyl or phenyl,

(VI) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl or a five- or six-membered carbocyclic or heterocyclic group, and the C1-4 alkyl group is optionally substituted by hydroxyl or C1-4 alkoxy,

(VII) $-NHCONHR^{VII}$ wherein R^{VII} represents C1-4 alkyl,

(VIII) $-OCOR^{VIII}$ wherein R^{VIII} represents C1-6 alkyl optionally substituted by amino group, or

(IX) $-NSO_2R^{IX}$ wherein R^{IX} represents C1-4 alkyl;

(11) $-NR^aR^b$;

(12) $-CO-OR^c$;

(13) $-CO-NR^dR^e$;

wherein, in groups (11) to (13), R^a, R^b, R^c, R^d, and R^e, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and the C1-4 alkyl group is optionally substituted by

(a) hydroxyl,

(b) a halogen atom,

(c) C1-4 alkoxy,

(d) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or

(e) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, and

R^d and R^e together may combine with the carbon atoms to which they are attached represent a saturated three- to nine-membered heterocyclic group, and the heterocyclic group is optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom or may contain one or more additional heteroatoms;

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to

nine-membered heterocyclic group;

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group;

(17) $-OCOR^k$ wherein R^k represents C1-4 alkyl; or

(18) $-OSO_2R^L$ wherein R^L represents C1-4 alkyl,

wherein (14) carbocyclic group, (15) heterocyclic group, and (16) bicyclic carbocyclic or heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) $-CO-OR^f$, or (xii) $-CO-NR^gR^h$ wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and

R^{10} and R^{11}, R^{11} and R^{12}, R^{12} and R^{13}, and R^{13} and R^{14} together may combine with the carbon atoms to which they are attached represent a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group, and the carbocyclic or heterocyclic group is optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) $-CO-OR^f$, or (xii) $-CO-NR^gR^h$ wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl,

provided that, when D^1, D^2, D^3, D^4, X, E, G, J, L, and M represent a nitrogen atom, groups R^2 to R^6 and R^{10} to R^{14} which attach to the nitrogen atom are absent, and

provided that, when all of D^1, D^2, D^3, and D^4 represent a carbon atom,

I) at least one of R^4 and R^5 represents (4) cyano group, (5) nitro group, (12) $-CO-OR^c$, (13) $-CO-NR^dR^e$ wherein any one of R^d and R^e represents optionally substituted C1-4 alkyl, (14) carbocyclic group, (15) heterocyclic group

wherein the heterocyclic group contains at least one substituent, or (16) bicyclic carbocyclic group or heterocyclic group, or

II) L represents a nitrogen atom, E, G, J, and M represent a carbon atom, R^{10} represents a hydrogen atom, and R^{14} represents (6) C1-6 alkyl group, (14) carbocyclic group, (15) heterocyclic group, or (16) bicyclic carbocyclic group or heterocyclic group.

[0015] In another embodiment of the present invention, formula (I) may also be defined as follow:

That is, in formula (I),

A represents a group of formula (a),

Z represents -O-, -N(-R^Z)-, -S-, or -C(=O)- wherein R^Z represents a hydrogen atom or unsubstituted C1-4 alkyl,

D^1, D^2, D^3, D^4, X, E, G, J, L, and M, which may be the same or different, represent C or N,

R^1 to R^6 and R^{10} to R^{14}, which may be the same or different, represent

(1) a hydrogen atom;

(2) a halogen atom;

(3) hydroxyl;

(4) cyano group;

(5) nitro group;

(6) C1-6 alkyl;

(7) C2-6 alkenyl;

(8) C2-6 alkynyl;

(9) C1-6 alkoxy;

(10) C1-6 alkylthio;

wherein (6) C1-6 alkyl, (7) C2-6 alkenyl, (8) C2-6 alkynyl, (9) C1-6 alkoxy, and (10) C1-6 alkylthio are optionally substituted by

(I) hydroxyl,

(II) a halogen atom,

(III) C1-4 alkoxy,

(IV) an oxygen atom,

(V) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group optionally

substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or

(VI) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, and the C1-4 alkyl group is optionally substituted by hydroxyl or C1-4 alkoxy,

(11) $-NR^aR^b$;

(12) $-CO-OR^c$;

(13) $-CO-NR^dR^e$;

wherein, in groups (11) to (13), R^a, R^b, R^c, R^d, and R^e, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and the C1-4 alkyl group is optionally substituted by

(a) hydroxyl,

(b) a halogen atom,

(c) C1-4 alkoxy,

(d) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or

(e) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, and

R^d and R^e together may combine with the carbon atoms to which they are attached represent a saturated three- to nine-membered heterocyclic group, and the heterocyclic group is optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom or may contain one or more additional heteroatoms;

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group;

wherein (14) carbocyclic group, (15) heterocyclic group, and (16) bicyclic carbocyclic or heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen

atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and

R^{10} and R^{11}, R^{11} and R^{12}, R^{12} and R^{13}, and R^{13} and R^{14} together may combine with the carbon atoms to which they are attached represent a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group, and the carbocyclic or heterocyclic group is optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl,

provided that, when D^1, D^2, D^3, D^4, X, E, G, J, L, and M represent a nitrogen atom, groups R^2 to R^6 and R^{10} to R^{14} which attach to the nitrogen atom are absent, and

provided that, when all of D^1, D^2, D^3, and D^4 represent a carbon atom,

I) at least one of R^4 and R^5 represents (4) cyano group, (5) nitro group, (12) -CO-OR^c, (13) -CO-NR^{d}R^e wherein any one of R^d and R^e represents optionally substituted C1-4 alkyl, (14) carbocyclic group, (15) heterocyclic group wherein the heterocyclic group contains at least one substituent, or (16) bicyclic carbocyclic group or heterocyclic group, or

II) L represents a nitrogen atom, E, G, J, and M represent a carbon atom, R^{10} represents a hydrogen atom, and R^{14} represents (6) C1-6 alkyl group, (14) carbocyclic group, (15) heterocyclic group, or (16) bicyclic carbocyclic group or heterocyclic group.

[0016] In one preferred embodiment of the present

invention, in formula (I), at least one of D^1 to D^4 represents a nitrogen atom.

[0017] In another preferred embodiment of the present invention, in formula (I),

all of D^1 to D^4 represent a carbon atom,

R^1 and R^2 represent a hydrogen atom,

R^3 and R^6, which may be the same or different, represent a hydrogen atom, a halogen atom, or C1-4 alkyl, and

R^4 and R^5, which may be the same or different, represent

(4) cyano group;

(5) nitro group;

(12) -CO-OR^c;

(13) -CO-NR^{d}R^e;

wherein, in groups (12) and (13), R^c, R^d, and R^e, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, provided that at least one of R^d and R^e represents C1-4 alkyl, and the C1-4 alkyl group is optionally substituted by

(a) hydroxyl,

(b) a halogen atom,

(c) C1-4 alkoxy,

(d) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or

(e) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl,

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group;

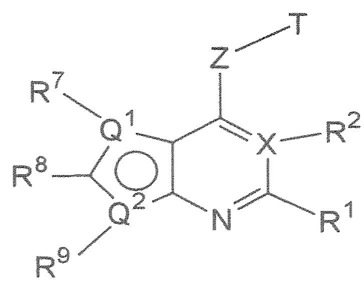
wherein (14) carbocyclic group, (15) heterocyclic group, and (16) bicyclic carbocyclic or heterocyclic

group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and

(15) heterocyclic group contains at least one substituent.

[0018] In one embodiment of the present invention, there are provided compounds of formula (II) or pharmaceutically acceptable salts or solvates thereof:

[Chemical formula 3]



(II)

wherein

T represents a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group,

wherein group T is optionally substituted by groups (2) to (16):

(2) a halogen atom;
(3) hydroxyl;
(4) cyano group;
(5) nitro group;
(6) C1-6 alkyl;
(7) C2-6 alkenyl;
(8) C2-6 alkynyl;
(9) C1-6 alkoxy;
(10) C1-6 alkylthio;

wherein (6) C1-6 alkyl, (7) C2-6 alkenyl, (8) C2-6 alkynyl, (9) C1-6 alkoxy, and (10) C1-6

alkylthio are optionally substituted by

(I) hydroxyl,

(II) a halogen atom,

(III) C1-4 alkoxy,

(IV) an oxygen atom,

(V) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or

(VI) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, and the C1-4 alkyl group is optionally substituted by hydroxyl or C1-4 alkoxy,

(11) $-NR^aR^b$;

(12) $-CO-OR^c$;

(13) $-CO-NR^dR^e$;

wherein, in groups (11) to (13), R^a, R^b, R^c, R^d, and R^e, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and the C1-4 alkyl group is optionally substituted by

(a) hydroxyl,

(b) a halogen atom,

(c) C1-4 alkoxy,

(d) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or

(e) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, and

R^d and R^e together may combine with the carbon atoms to which they are attached to represent a saturated three- to nine-membered heterocyclic group, and the heterocyclic group is optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom or may contain one or more additional heteroatoms;

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group;

wherein (14) carbocyclic group, (15) heterocyclic group, and (16) bicyclic carbocyclic or heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl,

two adjacent substituents on group T together may combine with the carbon atoms to which they are attached represent a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group, and the carbocyclic or heterocyclic group is optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl,

[0019] Q^1 and Q^2, which may be the same or different, represent C, S, O, or N,

X represents C or N,

Z represents -O-, -N(-R^Z)-, -S-, or -C(=O)- wherein R^Z represents a hydrogen atom or unsubstituted C1-4 alkyl,

R^1, R^2, and R^7 to R^9, which may be the same or different, represent,

(1) a hydrogen atom;

(2) a halogen atom;
(3) hydroxyl;
(4) cyano group;
(5) nitro group;
(6) C1-6 alkyl;
(7) C2-6 alkenyl;
(8) C2-6 alkynyl;
(9) C1-6 alkoxy;
(10) C1-6 alkylthio;

wherein (6) C1-6 alkyl, (7) C2-6 alkenyl, (8) C2-6 alkynyl, (9) C1-6 alkoxy, and (10) C1-6 alkylthio are optionally substituted by

(I) hydroxyl,
(II) a halogen atom,
(III) C1-4 alkoxy,
(IV) an oxygen atom,
(V) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or
(VI) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, and the C1-4 alkyl group is optionally substituted by hydroxyl or C1-4 alkoxy;

(11) $-NR^aR^b$;
(12) $-CO-OR^c$;
(13) $-CO-NR^dR^e$;

wherein, in groups (11) to (13), R^a, R^b, R^c, R^d, and R^e, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and C1-4 alkyl is optionally substituted by

(a) hydroxyl,
(b) a halogen atom,
(c) C1-4 alkoxy,
(d) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group

optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or

(e) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, and

R^d and R^e together may combine with the carbon atoms to which they are attached represent a saturated three- to nine-membered heterocyclic group, and the heterocyclic group is optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom and may contain one or more additional heteroatoms;

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group,

wherein (14) carbocyclic group, (15) heterocyclic group, and (16) bicyclic carbocyclic or heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and

the five-membered ring part containing Q^1 and Q^2 in formula (II) represents an aromatic ring,

provided that, when X represents a nitrogen atom, R^2 is absent, and

when Q^1 and Q^2 represent an oxygen atom or a sulfur atom, R^7 and R^9 which attach to the oxygen atom or the sulfur atom are absent, and, when both Q^1 and Q^2 represent a nitrogen atom, any one of R^7 and R^9 is absent.

[0020] The compounds according to the present invention

can be used for the treatment and prevention of diseases for which TGFβ inhibition is effective therapeutically or prophylactically.

Diseases for which TGFβ inhibition is effective therapeutically or prophylactically include, for example, chronic renal disease, acute renal disease, hepatic fibrosis, cirrhosis, pulmonary fibrosis, scleroderma, wound healing, arthritis, congestive cardiac disease, ulcer, ocular disorder, corneal problem, diabetic nephropathy, peritoneal sclerosis, arteriosclerosis, peritoneal adhesions, and subdermal adhesion and, further, malignant tumors.

Accordingly, the compounds according to the present invention can be useful for the prevention or treatment of these diseases. The compounds according to the present invention can also be useful for ex vivo expansion of hematopoietic stem cells.

The pharmaceutical composition according to the present invention comprises a compound of formula (I) or (II) according to the present invention as an active component.

The TGFβ inhibitor according to the present invention comprises a compound according to the present invention.

[0021] The method for treating or preventing a disease for which TGFβ inhibition according to the present invention is effective therapeutically or prophylactically, comprises the step of administering a therapeutically or prophylactically effective amount of a compound of formula (I) or (II) or a pharmaceutically acceptable salt or solvate thereof into a patient requiring the treatment or prevention of the disease for which TGFβ inhibition is effective therapeutically or prophylactically.

The method for ex vivo expansion according to the present invention comprises the step of adding a compound of formula (I) or (II) or a pharmaceutically acceptable salt or solvate thereof into intended cells in vitro to amplify the cells, at an amount effective for promoting cell growth.

DETAILED DESCRIPTION OF THE INVENTION

[0022] Compounds according to invention

The term "alkyl," "alkoxy," "alkenyl," "alkynyl," and "alkylthio" as used herein as a group or a part of a group respectively mean straight chain or branched chain alkyl, alkoxy, alkenyl, alkynyl, and alkylthio.

Accordingly, in the present specification, for example, "C1-6 alkyl" and "C1-6 alkoxy" as a group or a part of a group respectively mean straight chain or branched chain alkyl and alkoxy having 1 to 6 carbon atoms.

[0023] "C1-6 alkyl" is preferably C1-4 alkyl, more preferably C1-3 alkyl, still more preferably C1-2 alkyl. "C1-4 alkyl" is preferably C1-3 alkyl, more preferably C1-2 alkyl.

"C1-6 alkoxy" is preferably C1-4 alkoxy, more preferably C1-3 alkoxy, still more preferably C1-2 alkoxy. "C1-4 alkoxy" is preferably C1-3 alkoxy, more preferably C1-2 alkoxy.

[0024] "C2-6 alkenyl" is preferably C2-5 alkenyl, more preferably C2-4 alkenyl, still more preferably C2-3 alkenyl. "C2-4 alkenyl" is preferably C2-3 alkenyl, more preferably C2 alkenyl.

"C2-6 alkynyl" is preferably C2-5 alkynyl, more preferably C2-4 alkynyl, still more preferably C2-3 alkynyl. "C2-4 alkynyl" is preferably C2-3 alkynyl, more preferably C2 alkynyl.

"C1-6 alkylthio" is preferably C1-4 alkylthio, more preferably C1-3 alkylthio, still more preferably C1-2 alkylthio. "C1-4 alkylthio" is preferably C1-3 alkylthio, more preferably C1-2 alkylthio.

[0025] Examples of C1-6 alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, and n-hexyl.

Examples of C1-6 alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, and t-butoxy.

Examples of C2-6 alkenyl include allyl, butenyl, pentenyl, and hexenyl.

Examples of C2-6 alkynyl include 2-propynyl, butynyl, pentynyl, and hexynyl.

Examples of C1-6 alkylthio include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, i-butylthio, and s-butylthio.

[0026] In the present specification, alkyl "optionally substituted by" means either alkyl in which one or more hydrogen atoms on the alkyl group may be substituted by one or more substituents (which may be the same or different), or unsubstituted alkyl. It will be apparent to a person having ordinary skill in the art that the maximum number of substituents may be determined depending upon the number of substitutable hydrogen atoms on alkyl. This is true of groups that contain a group which is other than alkyl and is substitutable, for example, carbocyclic groups such as alkylthio, alkoxy, alkenyl, alkynyl, and phenyl, heterocyclic groups such as pyridyl, or bicyclic groups such as naphthyl.

[0027] Further, C1-6 alkyl optionally substituted by "an oxygen atom" mainly means such a state that one oxygen atom may be substituted for two hydrogen atoms on an identical carbon atom on alkyl, that is, the case where a ketone may be formed. This, however, does not exclude the case where a cyclic ether structure such as oxirane is formed. Accordingly, examples of C1-6 alkyl optionally substituted by "an oxygen atom" include ethan-1-one, propan-1-one, propan-2-one, butan-1-one, and butan-2-one. This is true of alkenyl, alkynyl, alkoxy, and alkylthio.

[0028] The term "halogen atom" as used herein means a fluorine, chlorine, bromine, or iodine atom.

[0029] The term "unsaturated carbocylic ring" and "unsaturated heterocyclic ring" means a carbocyclic or heterocyclic ring containing one or more unsaturated bonds such as a double bond.

[0030] The "saturated or unsaturated three- to

nine-membered carbocyclic group" is preferably a saturated or unsaturated five- to seven-membered carbocyclic group, more preferably a saturated or unsaturated five- or six-membered carbocyclic group. Examples of saturated or unsaturated three- to nine-membered carbocyclic rings include phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0031] The "saturated or unsaturated three- to nine-membered heterocyclic group" contains one or more heteroatoms selected from an oxygen atom, a nitrogen atom, and a sulfur atom. The saturated or unsaturated three- to nine-membered heterocyclic group is preferably a heterocyclic ring containing one, two or three heteroatoms and the remaining ring atoms being a carbon atom. The saturated or unsaturated three- to nine-membered heterocyclic group is preferably a saturated or unsaturated five- to seven-membered heterocyclic group, more preferably a saturated or unsaturated five- or six-membered heterocyclic group. Examples of saturated or unsaturated three- to nine-membered heterocyclic groups include thienyl, pyridyl, 1,2,3-triazolyl, thiazolyl, imidazolyl, isoxazolyl, pyrazolyl, piperazinyl, piperazino, piperidyl, piperidino, morpholinyl, morpholino, homopiperazinyl, homopiperazino, thiomorpholinyl, thiomorpholino, tetrahydropyrrolyl, and azepanyl.

[0032] When the carbocyclic or heterocyclic group is substituted by two alkyl groups, the two alkyl groups together may form an alkylene chain, preferably a C1-3 alkylene chain. Azabicyclo[2.2.2]octanyl, bicyclo[2.2.2]octanyl, and norbornanyl may be mentioned as the carbocyclic or heterocyclic group having the above crosslinked structure.

[0033] The "bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group" is preferably bicyclic saturated or unsaturated nine- or ten-membered carbocyclic or heterocyclic group. When the bicyclic group is a heterocyclic group, the bicyclic group contains one or more heteroatoms selected from oxygen, nitrogen, and sulfur atoms. Examples of such bicyclic groups

include indolizine, indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, benzothiazole, purine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, naphthyridine, and naphthalene.

[0034] In one preferred embodiment of the present invention, in formula (I), at least one of D^1 to D^4 represents a nitrogen atom. In this case, more preferably when at least one of D^1 and D^2 is a nitrogen atom, both D^3 and D^4 represent a carbon atom.

Still more preferably, D^1 represents a nitrogen atom, and all of D^2 to D^4 represent a carbon atom, or

D^2 represents a nitrogen atom, and all of D^1, D^3, and D^4 represent a carbon atom. In these cases, more preferably, X represents a carbon atom.

[0035] In formula (II), Q^1 and Q^2 are preferably selected from carbon and sulfur atoms. More preferably, any one of Q^1 and Q^2 represents a sulfur atom, and the other represents a carbon atom or a sulfur atom. Still more preferably,

Q^1 represents a sulfur atom, and Q^2 represents a carbon atom, or

Q^1 represents a carbon atom, and Q^2 represents a sulfur atom.

Still more preferably,

when Q^1 represents a carbon atom and, at the same time, Q^2 represents a sulfur atom, X represents a nitrogen atom, or

when Q^1 represents a sulfur atom and, at the same time, Q^2 represents a carbon atom, X represents a nitrogen atom, or

when Q^1 represents a sulfur atom and, at the same time, Q^2 represents a carbon atom, X represents a carbon atom.

[0036] Preferably, Z represents -O-, -NH-, -S-, or -C(=O)-, more preferably -O- or -NH-, still more preferably -O-.

[0037] Preferably, R^1, R^2, and R^3 independently represent a hydrogen atom, a halogen atom, or C1-4 alkyl, more preferably a hydrogen atom, a halogen atom, or methyl, still more preferably a hydrogen atom.

[0038] In one preferred embodiment of the present invention, when X represents a carbon atom, both R^1 and R^2

represent a hydrogen atom.

In this case, more preferably, when D^1 represents a nitrogen atom and, at the same time, all of D^2 to D^4 represent a carbon atom, R^6 represents a hydrogen atom.

Alternatively, in this case, more preferably when D^2 represents a nitrogen atom and, at the same time, all of D^1, D^3, and D^4 represent a carbon atom, R^3 represents a hydrogen atom or a halogen atom while R^6 represents a hydrogen atom.

[0039] R^4 and R^5, and R^7 to R^9, which may be the same or different, preferably represent

(1) a hydrogen atom ;

(2) a halogen atom;

(3) hydroxyl;

(6) C1-6 alkyl;

(9) C1-6 alkoxy;

(12) -CO-OR^c;

(13) -CO-NR^dR^e;

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group,

wherein these groups are optionally substituted as defined above.

[0040] More preferably, R^4 and R^5, and R^7 to R^9, which may be the same or different, represent

(1) a hydrogen atom;

(2) a halogen atom;

(6′) C1-4 alkyl optionally substituted by a halogen atom;

(9′) C1-4 alkoxy optionally substituted by a halogen atom;

(12′) -CO-OR^c;

(13′) -CO-NR^dR^e;

wherein, in groups (12′) and (13′), R^c, R^d, and

R^e, which may be the same or different, represent a hydrogen atom or C1-2 alkyl, and the C1-2 alkyl group is optionally substituted by

(a) hydroxyl,

(b) a halogen atom,

(d') a saturated or an unsaturated five- or six-membered carbocyclic or heterocyclic group, or

(e) amino;

(14′) a saturated or unsaturated five- or six-membered carbocyclic group; or

(15′) a saturated or unsaturated five- or six-membered heterocyclic group,

wherein (14′) carbocyclic group and (15′) heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0041] Still more preferably, R^4 and R^5, and R^7 to R^9, which may be the same or different, represent

(1) a hydrogen atom;

(2) a halogen atom;

(6) C1-6 alkyl; or

(9) C1-6 alkoxy;

wherein (6) C1-6 alkyl and (9) C1-6 alkoxy are optionally substituted as defined above.

[0042] More preferably, R^4 and R^5, and R^7 to R^9, which may be the same or different, represent a hydrogen atom, a halogen atom, or C1-4 alkyl.

[0043] In one more preferred embodiment of the present invention, R^4 and R^5 represent a hydrogen atom.

[0044] In another embodiment of the present invention,

R^4 represents optionally substituted C1-6 alkoxy, and R^5 represents a hydrogen atom, a halogen atom, or $-CO-NH_2$. More preferably, R^4 represents C1-6 alkoxy substituted by hydroxyl, still more preferably $-O(CH_2)m1-OH$ wherein m1 is an integer of 2 to 4, still more preferably $-OC_2H_5-OH$.

[0045] In a more preferred embodiment of the present invention, R^7 and R^9 represent a hydrogen atom, a halogen atom, or C1-4 alkyl, still more preferably a hydrogen atom, a halogen atom, or methyl.

[0046] In still more preferred embodiment of the present invention, R^8 represents

a hydrogen atom,

a halogen atom,

C1-4 alkyl,

a saturated or unsaturated six-membered carbocyclic group, or

a saturated or unsaturated six-membered heterocyclic group,

wherein the carbocyclic or heterocyclic group is optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0047] In a still more preferred embodiment of the present invention, R^7 and R^9 represent a hydrogen atom, a halogen atom, or C1-4 alkyl. In this case,

R^8 represents

a hydrogen atom,

a halogen atom,

C1-4 alkyl,

a saturated or unsaturated six-membered carbocyclic group, or

a saturated or unsaturated six-membered heterocyclic group,

wherein the carbocyclic and heterocyclic groups are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0048] In one preferred embodiment of the present invention, when X represents a carbon atom, both R^1 and R^2 represent a hydrogen atom.

In this case, more preferably, when Q^1 represents a sulfur atom and, at the same time, Q^2 represents a carbon atom, R^9 represents a hydrogen atom.

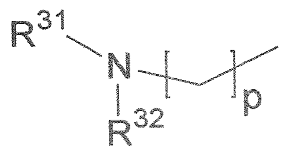
Alternatively, in this case, more preferably, when Q^1 represents a carbon atom and, at the same time, Q^2 represents a sulfur atom, R^7 represents a hydrogen atom.

[0049] In another embodiment of the present invention, R^4 and R^5, and R^7 to R^9 independently may represent group $-OR^X$ wherein R^X represents a hydrogen atom or $-(CH_2)m-R^{aX}$ wherein R^{aX} represents a hydrogen atom, a halogen atom, hydroxyl, a saturated or unsaturated three- to six-membered carbocyclic or heterocyclic group, C1-4 alkoxy, C1-4 alkoxycarbonyl, or $-NR^{bX}R^{cX}$ wherein R^{bx} and R^{cx}, which may be the same or different, represent a hydrogen atom, or C1-6 alkyl optionally substituted by hydroxyl, an oxygen atom, amino group, a nitrogen atom, or C1-4 alkyl, and R^{bX} and R^{cX} together may combine with nitrogen atoms to which they are attached represent a saturated or unsaturated five- or six-membered heterocyclic group wherein the heterocyclic group may contain one or more heteroatoms. The heterocyclic group is optionally substituted by C1-4 alkyl optionally substituted by hydroxyl; hydroxyl; an oxygen atom; aminocarbonyl; C1-4 alkoxy; C1-4 alkoxycarbonyl; or a saturated or unsaturated five- or six-membered heterocyclic group. The heterocyclic group may condense with another saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group to form a bicyclic group. m is an integer of 1 to 6. The alkyl chain part $-(CH_2)m-$ in this group is optionally substituted by hydroxyl; an oxygen atom; $-OR^{dX}$ wherein R^{dX} represents C1-4 alkyl or C1-4 alkylcarbonyl; or C1-4 alkyl optionally substituted by hydroxyl or a halogen atom.

[0050] In still another preferred embodiment of the present invention, R^4 and R^5, and R^7 to R^9 independently may represent group $-OR^m$ wherein R^m represents groups of formulae (i) to (vi):

(i) a group of formula (i):

[Chemical formula 4]



(i)

wherein

R^{31} and R^{32}, which may be the same or different, represent

a hydrogen atom, or

C1-6 alkyl optionally substituted by hydroxyl, an oxygen atom, amino group, or a nitrogen atom,

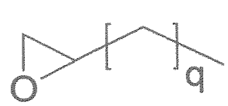
R^{31} and R^{32} together may combine with the nitrogen atom to which they are attached represent a saturated or unsaturated five- or six-membered heterocyclic group wherein the heterocyclic group may contain one or more additional heteroatoms and is optionally substituted by C1-4 alkyl optionally substituted by hydroxyl; hydroxyl; an oxygen atom; aminocarbonyl; C1-4 alkoxy; C1-4 alkoxycarbonyl; or a saturated or unsaturated five- or six-membered heterocyclic group, and, further, the heterocyclic group optionally formed by combining R^{31} with R^{32} may condense with another saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group to represent a bicyclic group,

p is an integer of 2 to 4, preferably 2 or 3, and

the alkyl chain part in this group is optionally substituted by hydroxyl or group $-OR^i$ wherein R^i represents C1-4 alkyl or C1-4 alkylcarbonyl;

[0051] (ii) a group of formula (ii):

[Chemical formula 5]

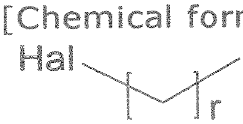


(ii)

wherein q is an integer of 1 to 4, preferably 1 or 2;

(iii) a group of formula (iii):

[Chemical formula 6]



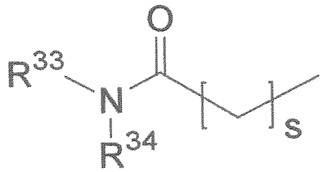
(iii)

wherein Hal represents a halogen atom, preferably a fluorine atom or a chlorine atom, and

r is an integer of 2 to 4, preferably 2 or 3;

[0052] (iv) a group of formula (iv):

[Chemical formula 7]


(iv)

wherein

R^{33} and R^{34}, which may be the same or different, represent

a hydrogen atom or

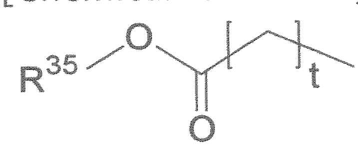
C_{1-6} alkyl optionally substituted by hydroxyl,

R^{33} and R^{34} may combine with the nitrogen atom to which they are attached represent a saturated or unsaturated five- or six-membered heterocyclic group wherein the heterocyclic group may contain one or more additional heteroatoms and is optionally substituted by C1-4 alkyl optionally substituted by hydroxyl; or a saturated or unsaturated five- or six-membered heterocyclic group, and, further, the heterocyclic group optionally formed by combining R^{33} with R^{34} may condense with another saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group to represent a bicyclic group, and

s is an integer of 0 to 3, preferably 0 to 2;

[0053] (v) a group of formula (v):

[Chemical formula 8]


(v)

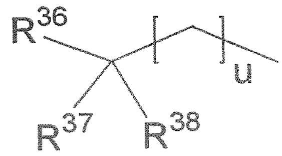
wherein

R^{35} represents C1-4 alkyl, and

t is an integer of 0 to 3, preferably 0 to 2; and

(vi) a group of formula (vi):

[Chemical formula 9]



(vi)

wherein

R^{36}, R^{37} and R^{38}, which may be the same or different, represent

a hydrogen atom,

C1-4 alkoxycarbonyl, or

C1-4 alkyl optionally substituted by hydroxyl or a halogen atom, and

u is an integer of 0 to 4, preferably 0 to 2, more preferably 0 or 1.

[0054] Preferably, R^6 represents a hydrogen atom, a halogen atom, or C1-4 alkyl, more preferably a hydrogen atom, a halogen atom, or methyl, still more preferably a hydrogen atom.

[0055] In a preferred embodiment of the present invention, in formula (I), when R^1 and R^2 represent a hydrogen atom, R^3 and R^6 represent a hydrogen atom, a halogen atom, or C1-4 alkyl. More preferably, all of R^1, R^2, R^3, and R^6 represent a hydrogen atom.

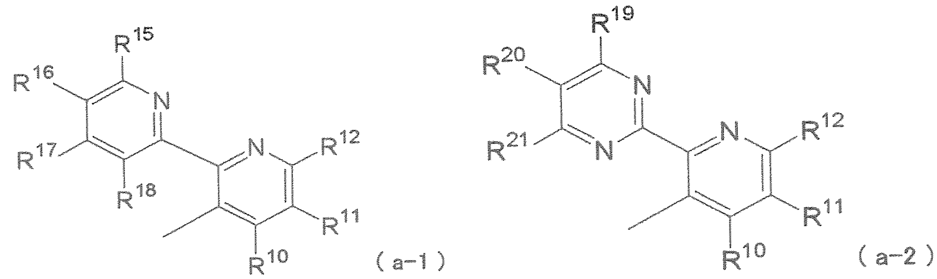
[0056] In one preferred embodiment of the present invention, in formula (I), when R^3 represents a hydrogen atom, Z represents -O-.

[0057] In a preferred embodiment of the present invention, in formula (II), both R^1 and R^2 represent a hydrogen atom.

[0058] In formula (I), when group A may represent a group of formula (a), preferably, in formula (a), any one of E, G, J, L, and M represents a nitrogen atom, and all the other groups represent a carbon atom. More preferably, L represents a nitrogen atom, and E, G, J and M represent a carbon atom.

[0059] In one preferred embodiment of the present invention, in formula (I), group A represents a group of formula (a-1) or (a-2):

[Chemical formula 10]



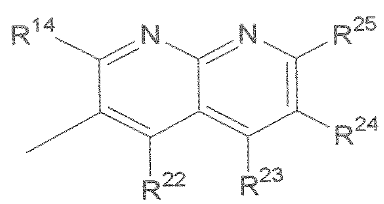
wherein

R^{10} to R^{12} are as defined above, and

R^{15} to R^{18} and R^{19} to R^{21}, which may be the same or different, represent (0) a hydrogen atom, (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl.

[0060] In another preferred embodiment of the present invention, in formula (I), group A represents a group of formula (a-3):

[Chemical formula 11]



(a−3)

wherein

R^{14} is as defined above, and

R^{22} to R^{25}, which may be the same or different, represent (0) a hydrogen atom, (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4

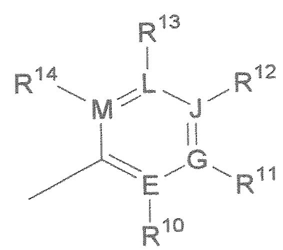
alkyl.

[0061] In formula (II), preferably, group T represents a unsaturated six-membered carbocyclic or heterocyclic group optionally substituted by groups (2) to (16), more preferably an unsaturated six-membered heterocyclic group optionally substituted by groups (2) to (16). In this case, the heteroatom in the heterocyclic group is preferably a nitrogen atom.

When the two adjacent substituents on group T together combine with the carbon atoms to which they are attached represent a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group, bicyclic groups which may be formed by group T include, for example, indolizine, indole, isoindole, benzofuran, benzothiophene, indazole, benzimidazole, benzothiazole, purine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, naphthyridine, and naphthalene.

[0062] In formula (II), more preferably, group T represents a group of formula (a):

[Chemical formula 12]



(a)

wherein

E, G, J, L, and M, which may be the same or different, represent C or N, and R^{10} to R^{14}, which may be the same or different, represent

(1) a hydrogen atom;

(2) a halogen atom;

(3) hydroxyl;

(4) cyano group;

(5) nitro group;

(6) C1-6 alkyl;

(7) C2-6 alkenyl;

(8) C2-6 alkynyl;

(9) C1-6 alkoxy;

(10) C1-6 alkylthio;

wherein (6) C1-6 alkyl, (7) C2-6 alkenyl, (8) C2-6 alkynyl, (9) C1-6 alkoxy, and (10) C1-6 alkylthio are optionally substituted by

(I) hydroxyl,

(II) a halogen atom,

(III) C1-4 alkoxy,

(IV) an oxygen atom,

(V) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or

(VI) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, and the C1-4 alkyl group is optionally substituted by hydroxyl or C1-4 alkoxy,

(11) $-NR^aR^b$;

(12) $-CO-OR^c$;

(13) $-CO-NR^dR^e$;

wherein, in groups (11) to (13), R^a, R^b, R^c, R^d, and R^e, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and the C1-4 alkyl group is optionally substituted by

(a) hydroxyl,

(b) a halogen atom,

(c) C1-4 alkoxy,

(d) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or

(e) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, and

R^d and R^e together may combine with the carbon atoms to which they are attached represent a saturated three- to nine-membered heterocyclic group, and the

heterocyclic group is optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom or may contain one or more additional heteroatoms;

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group;

wherein (14) carbocyclic group, (15) heterocyclic group, and (16) bicyclic carbocyclic or heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and

R^{10} and R^{11}, R^{11} and R^{12}, R^{12} and R^{13}, and R^{13} and R^{14} together may combine with the carbon atoms to which they are attached represent a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group, and the carbocyclic or heterocyclic group is optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl,

provided that, when E, G, J, L, and M represent a nitrogen atom, groups R^{10} to R^{14} which attach to the nitrogen atom are absent.

[0063] In formula (II), when group T may represent a group of formula (a), preferably, in formula (a), any one of E, G,

J, L, and M represents a nitrogen atom, and all the other groups represent a carbon atom. More preferably, L represents a nitrogen atom, and E, G, J and M represent a carbon atom.

[0064] In a further preferred embodiment of the present invention, in formula (II), group T represents a group of formula (a-1) or (a-2) wherein the substituents are as defined above. In another preferred embodiment of the present invention, in formula (II), group T represents a group of formula (a-3) wherein the substituents are as defined above.

[0065] In the group of formula (a-1) or (a-2) in formula (I) and formula (II), preferably, R^{15} to R^{18} and R^{19} to R^{21} are selected from the group consisting of a hydrogen atom, a halogen atom, C1-4 alkyl, and C1-4 alkoxy, more preferably selected from the group consisting of a hydrogen atom, a halogen atom, methyl, and methoxy. Still more preferably, all of these groups represent a hydrogen atom.

[0066] In the group of formula (a-3), preferably, R^{22} to R^{25} are selected from the group consisting of a hydrogen atom, a halogen atom, C1-4 alkyl, and C1-4 alkoxy, more preferably selected from the group consisting of a hydrogen atom, a halogen atom, and C1-4 alkyl, still more preferably selected from the group consisting of a hydrogen atom, a halogen atom, and methyl. Further preferably, all of R^{22} to R^{25} represent a hydrogen atom.

[0067] Preferably, R^{10} represents a hydrogen atom, a halogen atom, or methyl, more preferably a hydrogen atom.

[0068] In a preferred embodiment of the present invention, R^{11} and R^{12} independently are selected from the group consisting of a hydrogen atom, a halogen atom, and C1-4 alkyl, more preferably selected from the group consisting of a hydrogen atom and C1-4 alkyl. More preferably, at least one of R11 and R12 represents C1-4 alkyl and the other represents a hydrogen atom or C1-4 alkyl, still more preferably are selected from the group consisting of a hydrogen atom, methyl, and ethyl. More preferably, both R^{11} and R^{12} represent methyl. Alternatively, R^{11} represents a hydrogen atom, and R^{12}

represents methyl or ethyl.

[0069] In a more preferred embodiment of the present invention, when R^{11} and R^{12} are selected from the group consisting of a hydrogen atom, a halogen atom, C1-4 alkyl, and C1-4 alkoxy, preferably when selected from the group consisting of a hydrogen atom and C1-4 alkyl, R^{10} represents a hydrogen atom. Still more preferably, in the group of formula (a-1) or (a-2), R^{15} to R^{18} and R^{19} to R^{21} are selected from the group consisting of a hydrogen atom, a halogen atom, C1-4 alkyl, and C1-4 alkoxy. Most preferably, in the group of formula (a-1) or (a-2), all of R^{15} to R^{18} and R^{19} to R^{21} represent a hydrogen atom.

[0070] In another preferred embodiment of the present invention, R^{11} and R^{12} together combine with the carbon atoms to which they are attached represent a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group. In this case, preferably, R^{10} represents a hydrogen atom. More preferably, R^{11} and R^{12} together combine with the carbon atoms to which they are attached represent an unsaturated six-membered carbocyclic or heterocyclic group. Still more preferably, R^{11} and R^{12} together combine with the carbon atoms to which they are attached represent an unsaturated six-membered heterocyclic group.

[0071] When R^{10}, R^{11} and R^{12} are as defined above, in a preferred embodiment of the present invention, Z represents -O-, X represents a carbon atom, and R^{1} to R^{3} and R^{6} represent a hydrogen atom.

[0072] When R^{13} is present, R^{13} preferably represents a hydrogen atom, a halogen atom, or methyl, more preferably a hydrogen atom.

[0073] Preferably, R^{14} represents

optionally substituted C1-4 alkyl or

an optionally substituted saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group. Here regarding the C1-4 alkyl group, the term "optionally substituted" means that, as with "(6) C1-6 alkyl" in

formula (I) or formula (II), the alkyl group may be substituted. Further, the term "optionally substituted" in the carbocyclic or heterocyclic group means that, as with "(14) carbocyclic group" or "(15) heterocyclic group" in formula (I) or (II), the carbocyclic or heterocyclic group may be substituted.

[0074] When R^{11} and R^{12} are selected from the group consisting of a hydrogen atom, a halogen atom, C1-4 alkyl, and C1-4 alkoxy, preferably selected from the group consisting of a hydrogen atom and C1-4 alkyl, preferably R^{14} represents an optionally substituted saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group. In this case, more preferably, R^{14} represents an optionally substituted unsaturated six-membered heterocyclic group, still more preferably 2-pyridyl or 2,6-pyrimidyl.

[0075] When R^{11} and R^{12} together combine with the carbon atoms to which they are attached represent a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group, preferably, R^{14} represents optionally substituted C1-4 alkyl or an optionally substituted saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group. The C1-4 alkyl group which may be represented by R^{11} and R^{12} is preferably unsubstituted C1-4 alkyl. The carbocyclic or heterocyclic group which may be represented by R^{11} and R^{12} is preferably an optionally substituted unsaturated six-membered carbocyclic or heterocyclic group, more preferably phenyl optionally substituted by hydroxyl, a halogen atom, amino group, C1-4 alkyl, or C1-4 alkoxy, still more preferably phenyl optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0076] When A represents a group of formula (a-3),

R^{14} preferably represents

optionally substituted C1-4 alkyl,

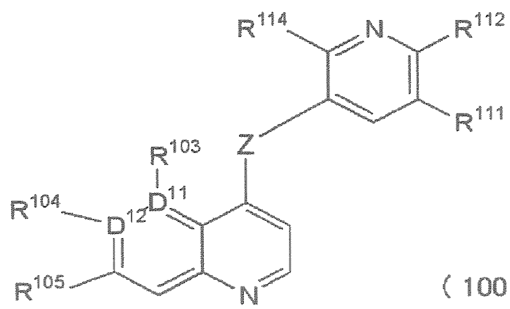
an optionally substituted, saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group, or

an optionally substituted bicyclic saturated or

unsaturated nine- or ten-membered carbocyclic or heterocyclic group. In a more preferred embodiment, R^{14} represents unsubstituted C1-4 alkyl. In another preferred embodiment, R^{14} represents an optionally substituted unsaturated six-membered carbocyclic or heterocyclic group, more preferably phenyl optionally substituted by hydroxyl, a halogen atom, amino group, C1-4 alkyl, or C1-4 alkoxy, still more preferably phenyl optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0077] In a preferred embodiment of the present invention, the compound of formula (I) may be a compound of formula (100):

[Chemical formula 13]



(100)

wherein

Z represents -O-, -NH-, -S-, or -C(=O)-, preferably -O- or -NH-, more preferably -O-,

any one of D^{11} and D^{12} represents a nitrogen atom, and the other represents a carbon atom,

R^{103} represents a hydrogen atom or a halogen atom, preferably a hydrogen atom,

R^{104} and R^{105}, which may be the same or different, represent

(1) a hydrogen atom ;

(2) a halogen atom;

(3) hydroxyl;

(6) C1-6 alkyl;

(9) C1-6 alkoxy;

(12) -CO-OR^c;

(13) -CO-NR^{d}R^e;

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group,

wherein these groups are optionally substituted as in the definition of formula (I),

R^{111} and R^{112}, which may be the same or different, are selected from the group consisting of a hydrogen atom, C1-4 alkyl, and C1-4 alkoxy, preferably selected from the group consisting of a hydrogen atom and C1-4 alkyl, more preferably selected from the group consisting of a hydrogen atom, methyl, and ethyl,

R^{114} represents

(14″) a saturated or unsaturated five- or six-membered carbocyclic group;

(15″) a saturated or unsaturated five- or six-membered heterocyclic group; or

(16″) a bicyclic saturated or unsaturated nine- or ten-membered carbocyclic or heterocyclic group;

wherein (14″) carbocyclic group, (15″) heterocyclic group, and (16″) bicyclic carbocyclic group or heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl.

[0078] In formula (100), preferably, when Z represents -O-, R^{103} represents a hydrogen atom.

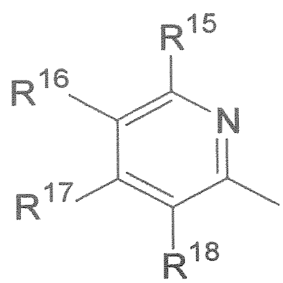
[0079] In formula (100), preferably, R^{104} and R^{105} represent a hydrogen atom, a halogen atom, or C1-4 alkyl,

more preferably a hydrogen atom, a halogen atom, or methyl, still more preferably a hydrogen atom.

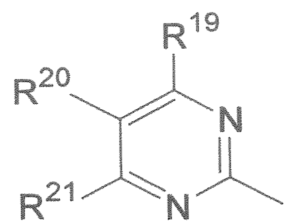
[0080] In formula (100), preferably, both R^{111} and R^{112} represent methyl, or alternatively R^{111} represents a hydrogen atom while R^{112} represents ethyl.

[0081] In formula (100), preferably, R^{114} represents a group of formula (a-4) or formula (a-5):

[Chemical formula 14]



(a-4)



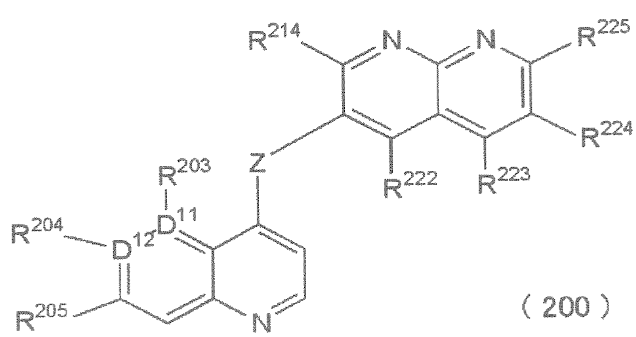
(a-5)

wherein

R^{15} to R^{18} and R^{19} to R^{21}, which may be the same or different, represent a group selected from the group consisting of a hydrogen atom, a halogen atom, C1-4 alkyl, and C1-4 alkoxy, preferably selected from the group consisting of a hydrogen atom, a halogen atom, C1-2 alkyl, and C1-2 alkoxy, and, more preferably, all of R^{15} to R^{18} and R^{19} to R^{21} represent a hydrogen atom.

[0082] In a preferred embodiment of the present invention, the compound of formula (I) may be a compound of formula (200):

[Chemical formula 15]



(200)

wherein

Z represents -O-, -NH-, -S-, or -C(=O)-, preferably -O- or -NH-, more preferably -O-,

any one of D^{11} and D^{12} represents a nitrogen atom, and the other represents a carbon atom,

R^{203} represents a hydrogen atom or a halogen atom, preferably a hydrogen atom,

R^{204} and R^{205}, which may be the same or different, represent

(1) a hydrogen atom ;

(2) a halogen atom;

(3) hydroxyl;

(6) C1-6 alkyl;

(9) C1-6 alkoxy;

(12) $-CO-OR^{c}$;

(13) $-CO-NR^{d}R^{e}$;

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group,

wherein these groups are optionally substituted as defined in formula (I),

R^{222} to R^{225}, which may be the same or different, represent a group selected from the group consisting of a hydrogen atom, a halogen atom, C1-4 alkyl, and C1-4 alkoxy, preferably a group selected from the group consisting of a hydrogen atom, a halogen atom, and C1-4 alkyl, more preferably a hydrogen atom, a halogen atom, or methyl, still more preferably a hydrogen atom, and

R^{214} represents

unsubstituted C1-4 alkyl,

an optionally substituted unsaturated six-membered carbocyclic or heterocyclic group, or

an optionally substituted, bicyclic saturated or unsaturated nine- or ten-membered carbocyclic or heterocyclic

group.

[0083] In formula (200), preferably, when Z represents -O- and, at the same time, R^{203} represents a hydrogen atom, all of R^{222} to R^{225} represent a hydrogen atom.

[0084] In formula (200), preferably, R^{204} and R^{205} represent a hydrogen atom, a halogen atom, or C1-4 alkyl, more preferably a hydrogen atom, a halogen atom, or methyl, still more preferably a hydrogen atom.

[0085] In a preferred embodiment of the present invention, in formula (200), R^{214} represents phenyl optionally substituted by hydroxyl, a halogen atom, amino group, C1-4 alkyl, or C1-4 alkoxy, more preferably phenyl optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy, still more preferably phenyl optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy, still more preferably unsubstituted phenyl.

[0086] In another preferred embodiment of the present invention, in formula (200), R^{214} represents methyl or ethyl.

[0087] In still another embodiment of the present invention, in formula (I), when all of D^1 to D^4 represent a carbon atom, requirement I) or II) should be satisfied:

I) any one of R^4 and R^5 represents (4) cyano group, (5) nitro group, (12) $-CO-OR^c$, (13) $-CO-NR^dR^e$ wherein any one of R^d and R^e represents optionally substituted C1-4 alkyl, (14) carbocyclic group, (15) heterocyclic group wherein the heterocyclic group contains at least one substituent, or (16) bicyclic carbocyclic or heterocyclic group; and

II) L represents a nitrogen atom, E, G, J, and M represent a carbon atom, R^{10} represents a hydrogen atom, and R^{14} represents (6) C1-6 alkyl group, (14) carbocyclic group,(15) heterocyclic group, or (16) bicyclic carbocyclic or heterocyclic group.

[0088] In another preferred embodiment of the present invention, in formula (I), when all of D^1 to D^4 represent a carbon atom, at least one of R^4 and R^5 represents (4) cyano

group, (5) nitro group, (12)-CO-OR^c, (14) carbocyclic group, (15) heterocyclic group containing at least one substituent, or (16) bicyclic carbocyclic or heterocyclic group.

[0089] In a further preferred embodiment of the present invention, in formula (I), when all of D^1 to D^4 represent a carbon atom,

R^1 and R^2 represent a hydrogen atom, and

R^4 and R^5, which may be the same or different, represent a hydrogen atom, a halogen atom, or C1-4 alkyl, and

R^4 and R^5, which may be the same or different, represent

(4) cyano group;

(5) nitro group;

(12) -CO-OR^c;

(13) -CO-NR^{d}R^e;

wherein, in groups (12) and (13), R^c, R^d, and R^e, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, provided that at least one of R^d and R^e represents C1-4 alkyl, and the C1-4 alkyl group is optionally substituted by

(a) hydroxyl,

(b) a halogen atom,

(c) C1-4 alkoxy,

(d) a saturated or unsaturated three- to nine-membered carbocyclic or heterocyclic group optionally substituted by C1-4 alkyl, C1-4 alkoxy, or a halogen atom, or

(e) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl,

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group,

wherein (14) carbocyclic group, (15)

heterocyclic group, and (16) bicyclic carbocyclic group or heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl, and (15) heterocyclic group contains at least one substituent. In this case, more preferably, R^4 and R^5 represent

-CO-NR^{d}R^e wherein R^d and R^e, which may be the same or different, represent a hydrogen atom or C1-2 alkyl optionally substituted by hydroxyl, a halogen atom, phenyl, or amino group; or

phenyl optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0090] In another preferred embodiment of the present invention, in formula (I), when all of D^1 to D^4 represent a carbon atom, at least one of R^4 and R^5 represents

an unsaturated five- or six-membered carbocyclic or heterocyclic group wherein the carbocyclic or heterocyclic group is optionally substituted by C1-4 alkyl, C1-4 alkoxy, a halogen atom ,amino group, or hydroxyl), or

a bicyclic unsaturated nine- or ten-membered carbocyclic or heterocyclic group wherein the carbocyclic or heterocyclic group is optionally substituted by C1-4 alkyl, C1-4 alkoxy, a halogen atom, amino group, or hydroxyl.

[0091] In still another preferred embodiment of the present invention, in formula (I), when all of D^1 to D^4 represent a carbon atom, R^1, R^2, R^3, R^4, R^5, and R^6 are as defined above. In this case, L represents a nitrogen atom, and E, G, J and M represent a carbon atom. Further, in this case, R^{14} represents (16) bicyclic carbocyclic or heterocyclic group in which these cyclic groups are optionally substituted as defined in formula (I).

[0092] In a further preferred embodiment of the present invention, in formula (I), when all of D^1 to D^4 represent a carbon atom, R^1, R^2, R^3, R^4, R^5, and R^6 are as defined above, L represents a nitrogen atom, and E, G, J and M represent a carbon atom. In this case, R^{14} represents

(6) C1-6 alkyl;

wherein the alkyl group is optionally substituted as defined in formula (I),

(14″) a saturated or unsaturated five- or six-membered carbocyclic group;

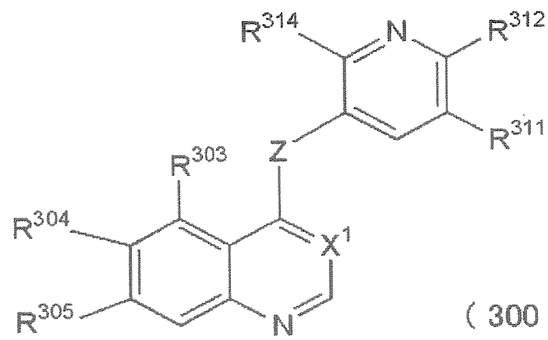
(15″) a saturated or unsaturated five- or six-membered heterocyclic group; or

(16″) a bicyclic saturated or unsaturated nine- or ten-membered carbocyclic or heterocyclic group;

wherein (14″) carbocyclic group, (15″) heterocyclic group, and (16″) bicyclic carbocyclic group or heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^gR^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl.

[0093] In another preferred embodiment of the present invention, in formula (I), when both D^1 and D^2 represent a carbon atom, the compound of formula (I) may be a compound of formula (300):

[Chemical formula 16]



(300)

wherein

X^1 represents CH or N,

Z represents -O-, -NH-, -S-, or -C(=O)-, preferably -O- or -NH-, more preferably -O-,

R^{303} represents a hydrogen atom, a halogen atom, or C1-4 alkyl, preferably a hydrogen atom, a halogen atom, or methyl, more preferably a hydrogen atom,

R^{304} and R^{305}, which may be the same or different, represent

(1) a hydrogen atom;

(2) a halogen atom;

(3) hydroxyl;

(6) C1-6 alkyl;

(9) C1-6 alkoxy;

(12) $-CO-OR^c$;

(13) $-CO-NR^dR^e$;

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group;

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group;

(17) $-OCOR^k$ wherein R^k represents C1-4 alkyl; or

(18) $-OSO_2R^L$ wherein R^L represents C1-4 alkyl,

wherein these groups are optionally substituted as defined in formula (I),

at least one of R^{311} and R^{312} represents C1-4 alkyl and the other represents a hydrogen atom or C1-4 alkyl, and

R^{314} represents an unsaturated six-membered heterocyclic group wherein the heterocyclic group is optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl.

[0094] In formula (300), preferably, when Z represents -O-, R^{303} represents a hydrogen atom and R^{314} represents a group of formula (a-4) or formula (a-5). In this case, in formula (a-4) or formula (a-5), preferably, R^{15} to R^{18} and R^{19} to R^{21} are selected from the group consisting of a hydrogen atom, a halogen atom, methyl and methoxy.

[0095] In a preferred embodiment of the present invention, in formula (300),

Z represents -O-,

R^{303} represents a hydrogen atom, and

R^{304} represents

(1) a hydrogen atom;

(2) a halogen atom;

(3) hydroxyl;

(9) C1-6 alkoxy;

(17) -OCOR^k wherein R^k represents C1-4 alkyl; or

(18) -OSO$_2$R^L wherein R^L represents C1-4 alkyl,

wherein these groups are optionally substituted as defined in claim 1,

R^{305} represents a hydrogen atom, a halogen atom, or -CO-NH$_2$, and

R^{314} represents a group of formula (a-4) or (a-5).

[0096] In formula (300), preferably, R^{15} to R^{18} and R^{19} to R^{21} represent a hydrogen atom.

[0097] In formula (300), preferably, X^1 represents CH.

[0098] In formula (300), preferably, R^{304} represents C1-6 alkoxy which is optionally substituted as defined in claim 1,

more preferably C1-6 alkoxy substituted by hydroxyl, still more preferably -O(CH_2)m1-OH wherein m1 is an integer of 2 to 4. Still more preferably, R^{304} represents -OC_2H_5-OH.

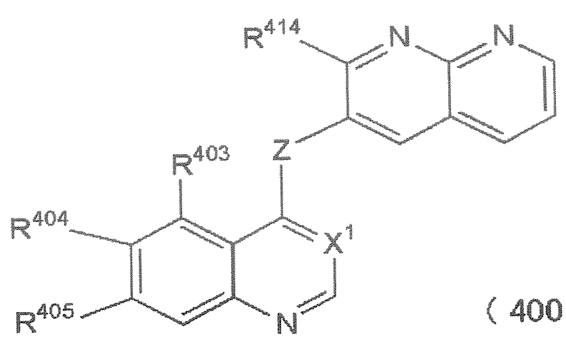
Prerferably, R^{305} represents a hydrogen atom, a fluorine atom, or -CO-NH_2.

[0099] In formula (300), preferably, R^{311} and R^{312}, which may be the same or different, represent C1-4 alkyl. More preferably, both R^{311} and R^{312} represent methyl. Alternatively, R^{311} represents a hydrogen atom and, at the same time, R^{312} represents C1-4 alkyl. Preferably, R^{311} represents a hydrogen atom, and, at the same time, R^{312} represents methyl or ethyl.

[0100] Preferred compounds of formula (300) are selected, for example, from compounds 181, 188, 192, 200, 202, and 205.

[0101] In another preferred embodiment of the present invention, in formula (I), when both D^1 and D^2 represent a carbon atom, the compund of formula (I) may be a compound of formula (400):

[Chemical formula 17]



(400)

wherein

X^1 represents CH or N,

Z represents -O-, -NH-, -S-, or -C(=O)-, preferably -O- or -NH-, more preferably -O-,

R^{403} represents a hydrogen atom, a halogen atom, or C1-4 alkyl, preferably a hydrogen atom, a halogen atom, or methyl, more preferably a hydrogen atom,

R^{404} and R^{405}, which may be the same or different, represent

(1) a hydrogen atom;
(2) a halogen atom;
(3) hydroxyl;
(6) C1-6 alkyl;
(9) C1-6 alkoxy;
(12) -CO-OR^c;
(13) -CO-NR^{d}R^e;
(14) a saturated or unsaturated three- to nine-membered carbocyclic group;
(15) a saturated or unsaturated three- to nine-membered heterocyclic group;
(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group;
(17) -OCOR^k wherein R^k represents C1-4 alkyl; or
(18) -OSO$_2$R^L wherein R^L represents C1-4 alkyl,
wherein these groups are optionally substituted as defined in formula (I),
R^{414} represents
(6) C1-6 alkyl;
wherein the alkyl group is optionally substituted as defined in formula (I),
(14'') a saturated or unsaturated five- or six-membered carbocyclic group;
(15'') a saturated or unsaturated five- or six-membered heterocyclic group; or
(16'') a bicyclic saturated or unsaturated nine- or ten-membered carbocyclic or heterocyclic group;

wherein (14'') carbocyclic group, (15'') heterocyclic group, and (16'') bicyclic carbocyclic group or heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom

or C1-4 alkyl.

[0102] In formula (400), preferably, when Z represents -O-, R^{403} represents a hydrogen atom, and

R^{414} represents

an unsaturated five- or six-membered carbocyclic or heterocyclic group wherein the carbocyclic or heterocyclic group is optionally substituted by C1-4 alkyl, C1-4 alkoxy, a halogen atom, amino group, or hydroxyl, or

a bicyclic unsaturated nine- or ten-membered carbocyclic or heterocyclic group wherein the carbocyclic or heterocyclic group is optionally substituted by C1-4 alkyl, C1-4 alkoxy, a halogen atom, amino group, or hydroxyl. In this case, more preferably, R^{414} represents phenyl optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0103] In a preferred embodiment of the present invention, in formula (400),

X^1 represents CH,

Z represents -O-,

R^{403} represents a hydrogen atom,

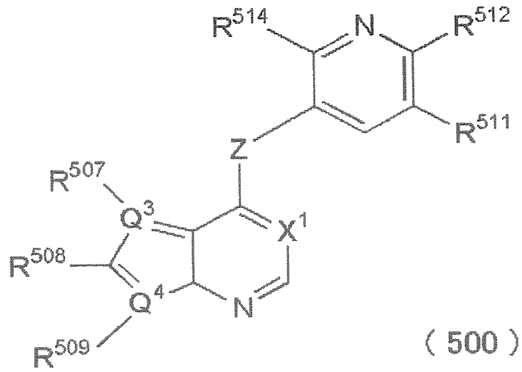
any one of R^{404} and R^{405} represents C1-4 alkoxy substituted by hydroxyl, and the other represents unsubstituted C1-4 alkoxy, and

R^{414} represents phenyl.

[0104] For example, compound 178 may be mentioned as preferred compounds of formula (400).

[0105] In a preferred embodiment of the present invention, the compound of formula (II) may be a compound of formula (500):

[Chemical formula 18]



(500)

wherein

X^1 represents CH or N,

Z represents -O-, -NH-, -S-, or -C(=O)-, preferably -O- or -NH-, more preferably -O-,

any one of Q^3 and Q^4 represents a sulfur atom, and the other represents a carbon atom,

R^{507} to R^{509}, which may be the same or different, represent

(1) a hydrogen atom;

(2) a halogen atom;

(3) hydroxyl;

(6) C1-6 alkyl;

(9) C1-6 alkoxy;

(12) -CO-OR^c;

(13) -CO-NR^{d}R^e;

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group

wherein these groups are optionally substituted as defined in formula (II),

R^{511} and R^{512}, which may be the same or different, are selected from the group consisting of a hydrogen atom and C1-4 alkyl, preferably selected from the group consisting of a hydrogen atom, methyl, and ethyl,

R^{514} represents

(14″) a saturated or unsaturated five- or six-membered carbocyclic group;

(15″) a saturated or unsaturated five- or six-membered heterocyclic group; or

(16″) a bicyclic saturated or unsaturated nine- or ten-membered carbocyclic or heterocyclic group;

wherein (14″) carbocyclic group, (15″) heterocyclic group, and (16″) bicyclic carbocyclic group or heterocyclic group are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino groups are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which may be the same or different, represent a hydrogen atom or C1-4 alkyl.

[0106] In formula (500), preferably,

when Q^3 represents a sulfur atom, Q^4 represents a carbon atom, or

when Q^3 represents a carbon atom, Q^4 represents a sulfur atom.

[0107] In formula (500), both R^{511} and R^{512} represent methyl, or alternatively, R^{511} represents a hydrogen atom while R^{512} represents ethyl. In this case, preferably, Z represents -O-.

[0108] In formula (500), preferably, R^{514} represents a group of formula (a-4) or formula (a-5). In formula (a-4) or formula (a-5), R^{15} to R^{18} and R^{19} to R^{21}, which may be the same or different, are selected from the group consisting of a hydrogen atom, a halogen atom, C1-4 alkyl, and C1-4 alkoxy. Preferably, all of R^{15} to R^{18} and R^{19} to R^{21} represent a hydrogen atom.

[0109] Preferably, R^{507} and R^{509} represent a hydrogen atom, a halogen atom, or C1-4 alkyl, more preferably a hydrogen atom, a halogen atom, or methyl, still more preferably a hydrogen atom.

[0110] Preferably, R^{508} represents

a hydrogen atom,

a halogen atom,

C1-4 alkyl, or

a saturated or unsaturated six-membered carbocyclic or,

a saturated or unsaturated six-membered heterocyclic group,

wherein said carbocyclic or heterocyclic group is optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0111] In formula (500), preferably,

R^{507} and R^{509} represent a hydrogen atom, a halogen atom, or C1-4 alkyl, and, in this case,

R^{508} represents

a hydrogen atom ,

a halogen atom,

C1-4 alkyl,

a saturated or unsaturated six-membered carbocyclic group, or

a saturated or unsaturated six-membered heterocyclic group

wherein the carbocyclic and heterocyclic groups are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0112] In a preferred embodiment of the present invention, in formula (500),

Q^3 represents a sulfur atom,

Q^4 represents a carbon atom,

R^{508} represents

a hydrogen atom,

C1-4 alkyl, or

a saturated or unsaturated six-membered carbocyclic or heterocyclic group,

wherein said carbocyclic or heterocyclic group is optionally substituted by (i) hydroxyl, (ii) a halogen

atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy, and

R^{509} represents a hydrogen atom. In this case, more preferably, R^{508} represents a hydrogen atom or phenyl.

[0113] In a preferred embodiment of the present invention, in formula (500),

Q^3 represents a carbon atom,

Q^4 represents a sulfur atom, and

R^{507} and R^{508} are selected from the group consisting of a hydrogen atom and C1-4 alkyl. In this case, more preferably,

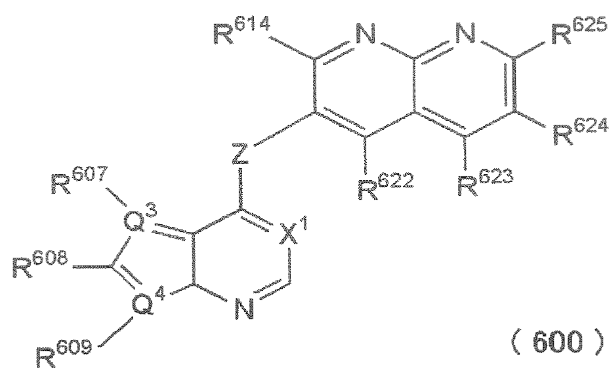
both R^{507} and R^{508} represent a hydrogen atom or

both R^{507} and R^{508} represent methyl or

R^{507} represents methyl while R^{508} represents a hydrogen atom.

[0114] In a preferred embodiment of the present invention, the compound of formula (II) may be a compound of formula (600):

[Chemical formula 19]



(600)

wherein

X^1 represents CH or N,

Z represents -O-, -NH-, -S-, or -C(=O)-,

any one of Q^3 and Q^4 represents a sulfur atom, and the other represents a carbon atom,

R^{607} to R^{609}, which may be the same or different, represent

(1) a hydrogen atom;

(2) a halogen atom;

(3) hydroxyl;

(6) C1-6 alkyl;

(9) C1-6 alkoxy;

(12) -CO-OR^{c};

(13) -CO-NR^{d}R^{e};

(14) a saturated or unsaturated three- to nine-membered carbocyclic group;

(15) a saturated or unsaturated three- to nine-membered heterocyclic group; or

(16) a bicyclic saturated or unsaturated eight- to twelve-membered carbocyclic or heterocyclic group,

wherein these groups are optionally substituted as defined in formula (II),

R^{622} to R^{625}, which may be the same or different, are selected from the group consisting of a hydrogen atom, a halogen atom, C1-4 alkyl, and C1-4 alkoxy, and

R^{614} represents

unsubstituted C1-4 alkyl,

an optionally substituted unsaturated six-membered carbocyclic or heterocyclic group, or

an optionally substituted bicyclic saturated or unsaturated nine- or ten-membered carbocyclic or heterocyclic group.

[0115] In formula (600), preferably,

when Q^{3} represents a sulfur atom, Q^{4} represents a carbon atom, or

when Q^{3} represents a carbon atom, Q^{4} represents a sulfur atom.

[0116] In formula (600), when Z represents -O-, preferably, all of R^{622} to R^{625} represent a hydrogen atom.

[0117] In a preferred embodiment of the present invention, in formula (600), R^{614} represents phenyl optionally substituted by hydroxyl, a halogen atom, amino group, C1-4 alkyl, or C1-4 alkoxy, more preferably phenyl optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy, still more preferably unsubstituted phenyl.

[0118] In another preferred embodiment of the present invention, in formula (600), R^{614} represents methyl or ethyl.

[0119] Preferably, R^{607} and R^{609} represent a hydrogen atom, a halogen atom, or C1-4 alkyl, more preferably a hydrogen atom, a halogen atom, or methyl, more preferably a hydrogen atom.

[0120] Preferably, R^{608} represents

a hydrogen atom,

a halogen atom,

C1-4 alkyl,

a saturated or unsaturated six-membered carbocyclic group, or

a saturated or unsaturated six-membered heterocyclic group,

wherein the carbocyclic and heterocyclic groups are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0121] In formula (600), preferably, R^{607} and R^{609} represent a hydrogen atom, a halogen atom, or C1-4 alkyl

R^{608} represents

a hydrogen atom,

a halogen atom,

C1-4 alkyl,

a saturated or unsaturated six-membered carbocyclic group, or

a saturated or unsaturated six-membered heterocyclic group,

wherein the carbocyclic and heterocyclic groups are optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy.

[0122] In a preferred embodiment of the present invention, in formula (600),

Q^3 represents a sulfur atom,

Q^4 represents a carbon atom,

R^{608} represents

a hydrogen atom,

C1-4 alkyl, or

a saturated or unsaturated six-membered carbocyclic or heterocyclic group,

wherein said carbocyclic or heterocyclic group is optionally substituted by (i) hydroxyl, (ii) a halogen atom, (v') amino group, (vi') C1-2 alkyl, or (ix') C1-2 alkoxy, and

R^{609} represents a hydrogen atom. In this case, more preferably, R^{608} represents a hydrogen atom or phenyl.

[0123] In a preferred embodiment of the present invention, in formula (600),

Q^3 represents a carbon atom,

Q^4 represents a sulfur atom, and

R^{607} and R^{608} are selected from the group consisting of a hydrogen atom and C1-4 alkyl. In this case, more preferably,

both R^{607} and R^{608} represent a hydrogen atom or

both R^{607} and R^{608} represent methyl or

R^{607} represents methyl while R^{608} represents a hydrogen atom.

[0124] More preferred compounds of the present invention include compounds described in Examples.

When the compounds of the present invention are compounds of formula (I), the compounds are preferably selected from the group consisting of compounds 1 to 27, 30, 31, 37 to 70, 73, 74, 81 to 179 and 181 to 225, more preferably compounds 1, 4, 6, 13, 16, 18, 27, 30, 37, 49, 50, 51, 56, 66, 103, 110, 117, 126, 133, 140 to 145, 155, 158, 159, 161, 162, 174 to 178, 181, 188, 192, 200, 202 and 205, still more preferably compounds 37, 142, 178, 181, 188, 192, 200, 202 and 205.

When the compounds of the present invention are compounds of formula (II), the compounds are preferably selected from the group consisting of compounds 28, 29, 32 to 35, 71, 72, 75 to 78 and 180, more preferably compounds 28, 32 and 33.

[0125] Salts or solvates of compounds

The compounds according to the present invention may form pharmaceutically acceptable salts thereof. Preferred examples of such salts include: alkali metal or alkaline earth metal salts such as sodium salts, potassium salts or calcium salts; hydrohalogenic acid salts such as hydrofluoride salts, hydrochloride salts, hydrobromide salts, or hydroiodide salts; inorganic acid salts such as nitric acid salts, perchloric acid salts, sulfuric acid salts, or phosphoric acid salts; lower alkylsulfonic acid salts such as methanesulfonic acid salts, trifluoromethanesulfonic acid salts, or ethanesulfonic acid salts; arylsulfonic acid salts such as benzenesulfonic acid salts or p-toluenesulfonic acid salts; organic acid salts such as fumaric acid salts, succinic acid salts, citric acid salts, tartaric acid salts, oxalic acid salts, maleic acid salts, acetic acid salts, malic acid salts, lactic acid salts, or ascorbic acid salts; and amino acid salts such as glycine salts, phenylalanine salts, glutamic acid salts, or aspartic acid salts.

The compounds according to the present invention may form solvates. Such solvates include, for example, hydrates, alcoholates, for example, methanolates and ethanolates, and etherates, for example, diethyl etherates.

[0126] Production of compounds according to the present invention

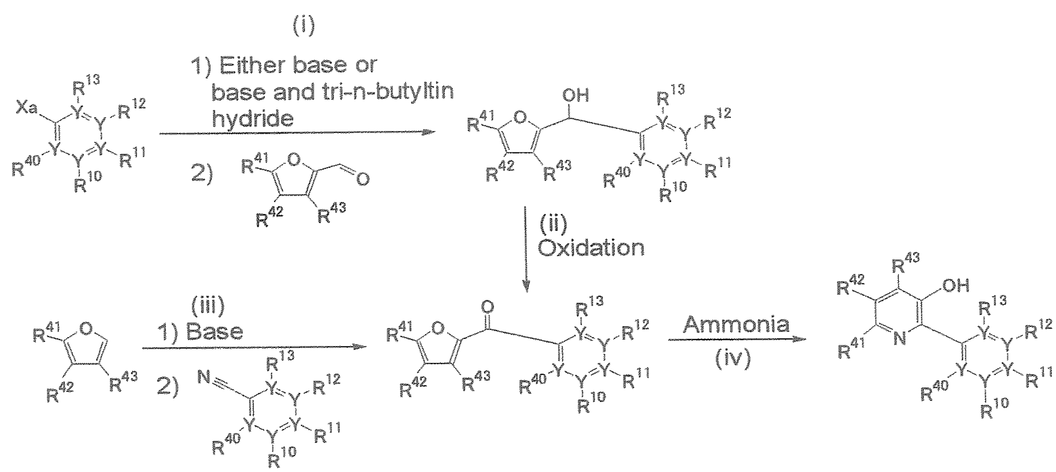
The compounds according to the present invention can be produced, for example, according to schemes 1 to 19. Quinoline derivatives or quinazoline derivatives of Reference Examples having structures similar to the compounds according to the present invention can be produced, for example, according to schemes r1 to r34 which will be described later. Further, the compounds according to the present invention may also be synthesized by conventional methods described, for example, in WO 2000/43366 and WO 2004/018430. In the present invention, starting compounds necessary for the synthesis of the compounds according to the present invention

are commercially available or alternatively can be easily produced by conventional methods.

[0127] Scheme 1

Bipyridine derivatives as a partial structure of the compounds according to the present invention can be produced, for example, accoridng to scheme 1.

[Chemical formula 20]



wherein

R^{10} to R^{13} are as defined above,

R^{40} and Xa are selected from groups as defined in R^{10}, and

R^{41} ro R^{43} are selected from groups as defined in R^{15}, and

Y's each independently represent C or N.

[0128] In this scheme, the aimed compounds can be synthesized through the following two routes:

(I) A ketone derivative can be produced by reacting an allyl halogen derivative with a base, for example, n-butyllithium, either directly or after conversion to a trialkyltin compound, for example, using tri-n-butyltin hydride, reacting the resultant compound with a furfural derivative (step (i)) to give an alcohol derivative, and then oxidizing the alcohol derivative with a suitable oxidizing agent, for example, manganese dioxide (step (ii)).

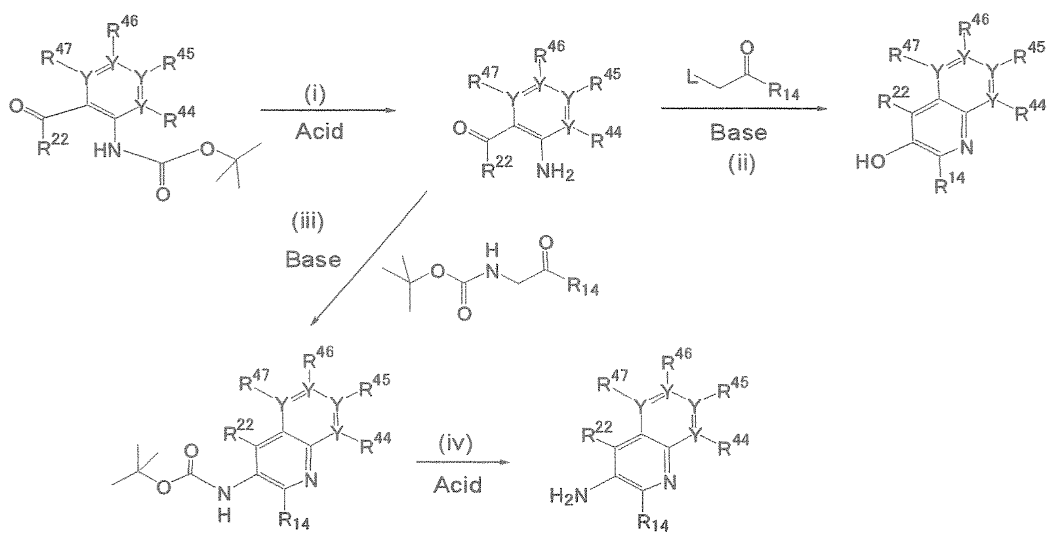
(II) A ketone derivative can be produced by reacting a furan derivative with an alkyllithium reagent, for example, n-butyllithium, and then reacting the resultant compound with an acylating agent (step (iii)).

The aimed compounds can be produced by reacting the ketone derivative produced in the above step (I) or (II) with ammonia (step (iv)).

[0129] Scheme 2

Naphthyridine derivatives as a partial structure of the compounds according to the present invention can be produced, for example, according to scheme 2.

[Chemical formula 21]



wherein

R^{14} and R^{22} are as defined above,

R^{44} to R^{47} are selected from groups defined in R^{23}, and

Y's each independently represent C or N.

[0130] The aimed 3-hydroxypyridine derivatives can be produced by deprotecting an aniline derivative in which the amino group has been protected (step (i)), and reacting the resultant o-acylaniline derivative with a methyl ketone derivative (step (ii)).

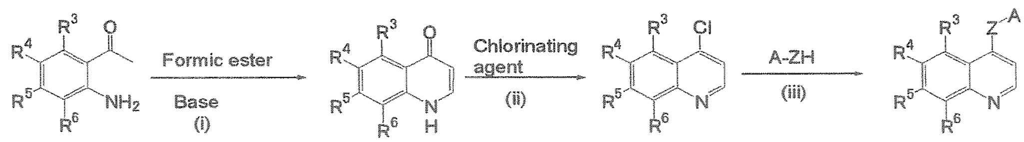
The aimed 3-aminopyridine derivatives can be produced by reacting the o-acylaniline derivative produced above with an aminomethyl ketone derivative in which the amino group has been protected (step (iii)), and then deprotecting the resultant compound, that is, removing the amino group from the resultant compound (step (iv)).

[0131] Schemes 3 and 4

The quinoline derivatives according to the present invention can be produced, for example, according to scheme 3 or 4.

Scheme 3:

[Chemical formula 22]

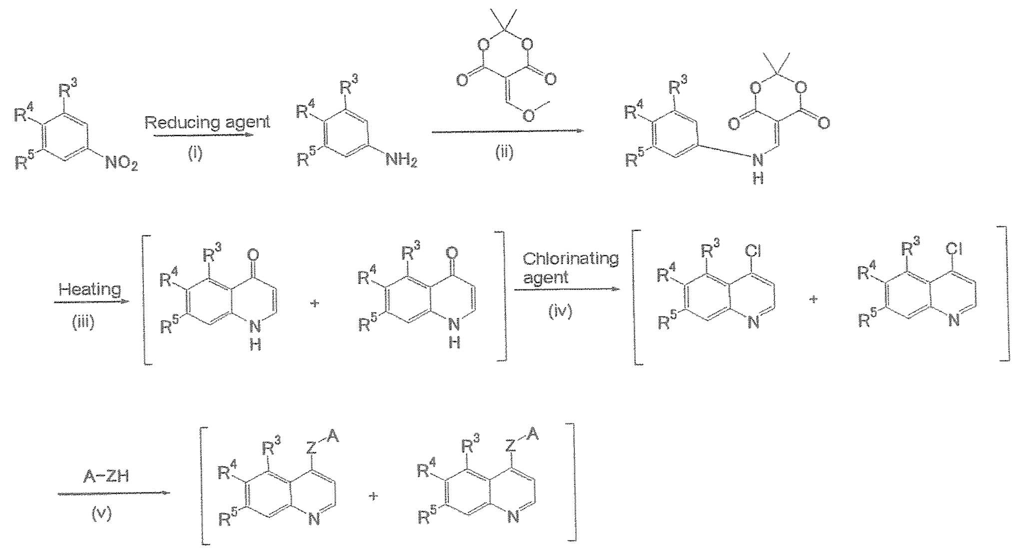


wherein the substituents are as defined above.

[0132] In scheme 3, the quinolone derivatives as an intermediate can be synthesized, for example, according to WO 97/17329. The 4- chloroquinoline derivatives can be synthesized by a conventional method described, for example, in Org. Synth. Col. Vol.3, 272 (1955), Acta Chim. Hung., 112, 241 (1983), or WO 98/47873. The aimed compounds can be synthesized by reacting the resultant 4- chloroquinoline derivative with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative in a suitable solvent, for example, 1,2-dichlorobenzene, or in a system free from a solvent in the presence of a suitable base, for example, 4-dimethylaminopyridine (step (iii)).

[0133] Scheme 4:

[Chemical formula 23]



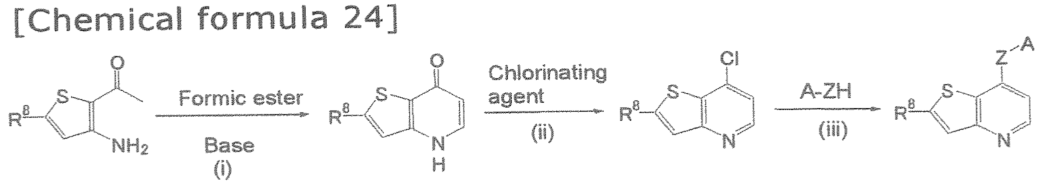
wherein the substituents are as defined above.

[0134] In scheme 4, the 4-chloroquinoline derivatives as an intermediate can be synthesized by a conventional method described, for example, in WO 00/50405. The aimed compounds can be synthesized by reacting the resultant 4-chloroquinoline derivative with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative in a suitable solvent, for example, 1,2-dichlorobenzene, or in a system free from a solvent in the presence of a suitable base, for example, 4-dimethylaminopyridine (step (v)).

[0135] Scheme 5

The thiazopyridine derivatives according to the present invention can be produced, for example, according to scheme 5.

[Chemical formula 24]



wherein the substituents are as defined above.

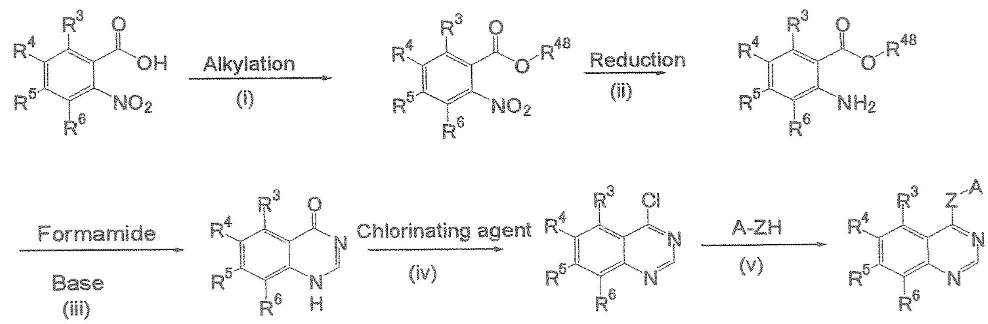
[0136] The aimed compounds can be synthesized by reacting an acetyl-amino-thiophene derivative with a formic ester in the presence of a suitable base, for example, sodium methoxide (step (i)), reacting the resultant thienopyridin-7-one derivative with a suitable chlorinating agent, for example,

phosphorus oxychloride (step (ii)), and reacting the resultant 7-chlorothienopyridine derivative with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative in a suitable solvent, for example, 1,2-dichlorobenzene, or in a solvent-free system in the presence of a suitable base, for example, 4-dimethylaminopyridine (step (iii)).

[0137] Scheme 6

The quinazoline derivatives according to the present invention can be produced, for example, according to scheme 6.

[Chemical formula 25]



wherein

R^{48} represents a group suitable for the cyclization reaction in step (iii), and

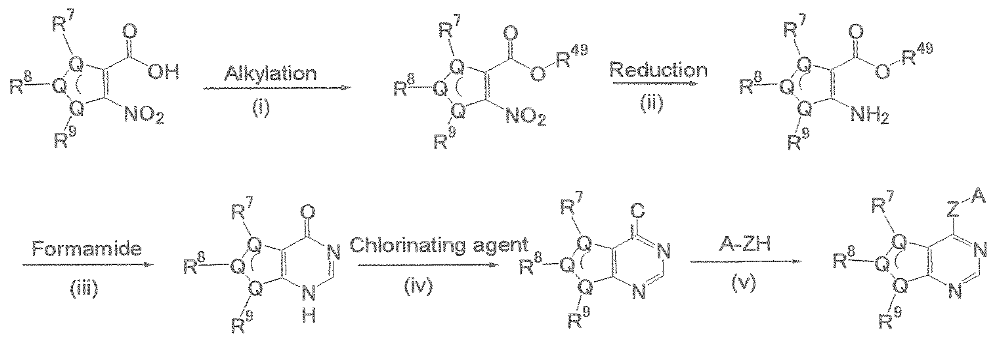
the other substituents are as defined above.

[0138] The 4-chloroquinazoline derivatives can be synthesized by a conventional method described, for example, in J. Am. Chem. Soc., 68, 1299 (1946), J. Am. Chem. Soc., 68, 1305 (1946), and Dai Yuki Kagaku (Comprehensive Organic Chemistry), Editor, Kotake, Vol. 17, p. 150, Asakura Publishing Co., Ltd. (published in 1967). The aimed compounds can be synthesized by reacting the resultant 4-chloroquinazoline derivative with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative in a suitable solvent, for example, 1,2-dichlorobenzene, or in a solvent-free system, in the presence of a suitable base, for example, 4-dimethylaminopyridine (step (v)).

[0139] Scheme 7

The heterocondensed ring-type pyrimidine derivatives according to the present invevntion can be produced, for example, according to scheme 7.

[Chemical formula 26]



wherein

R^{49} represents a group suitable for the cyclization reaction in step (iii),

Q's each independently represent C, S, or N, and

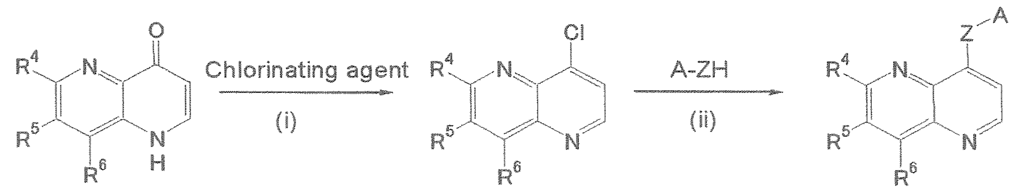
the other substituents are as defined above.

[0140] The aimed compounds can be produced by reacting an o-nitrocarboxylic acid derivative with a suitable alkylating agent, for example, methyl iodide (step (i)), reducing the nitro group in the resultant compound with a suitable reducing agent, for example, palladium hydroxide/a hydrogen gas) (step (ii)) to give an o-aminocarboxylic ester, reacting the o-aminocarboxylic ester with formamide (step (iii)), reacting the resultant compound with a suitable chlorinating agent, for example, phosphorus oxychloride (step (iv)), and reacting the resultant chloropyrimidine derivative with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative in a suitable solvent, for example, 1,2-dichlorobenzene, or in a solvent-free system in the presence of a suitable base, for example, 4-dimethylaminopyridine (step (v)).

[0141] Scheme 8

The 1,5-naphthyridine derivatives according to the present invention can be produced, for example, according to scheme 9.

[Chemical formula 27]



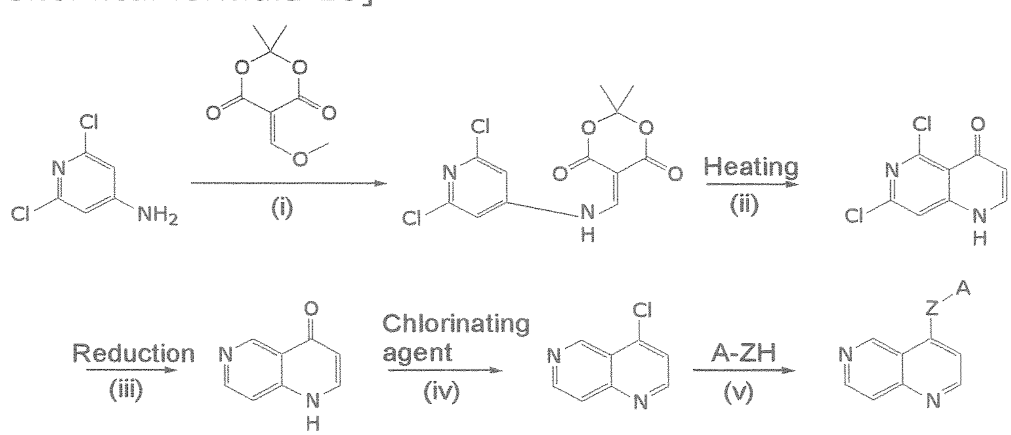
wherein the substituents are as defined above.

[0142] The 4-naphthyridinone derivatives can be synthesized in the same manner as shown, for example, in scheme 3 or 4. The aimed compounds can be synthesized by reacting the 4-naphthyridinone derivative with a suitable chlorinating agent, for example, phosphorus oxychloride (step (i)), and reacting the resultant chloronaphthyridine derivative with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative in a suitable solvent, for example, 1,2-dichlorobenzene, or in a solvent-free system in the presence of a suitable base, for example, 4-dimethylaminopyridine (step (ii)).

[0143] Scheme 9

The 1,6-naphthyridine derivatives according to the present invention can be produced, for example, according to scheme 9.

[Chemical formula 28]



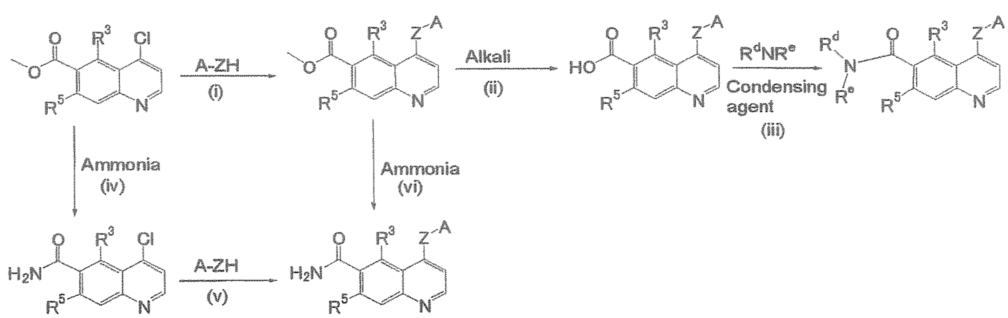
[0144] The aimed compounds can be synthesized by reacting an 4-amino-2,6-dichloropyridine with

5-methoxymethylene-2,2-dimethyl-[1,3]dioxan-4,6-dione (step (i)), further heating the mixture, for example, at 220°C for one hr (step (ii)), reducing the resultant compound with a suitable reducing agent, for example, palladium hydroxide/a hydrogen gas (step (iii)) to give a [1,6]naphthyridinone derivative, reacting the [1,6]naphthyridinone derivative with a suitable chlorinating agent, for example, phosphorus oxychloride (step (i)), and reacting the resultant chloronaphthyridine derivative with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative in a suitable solvent, for example, 1,2-dichlorobenzene, or in a solvent-free system in the presence of a suitable base, for example, 4-dimethylaminopyridine (step (ii)).

[0145] Scheme 10

The 6-amidoquinoline derivatives according to the present invention can be produced, for example, according to scheme 10.

[Chemical formula 29]



wherein the substituents are as defined above.

[0146] The N-monosubstituted or N-disubstituted amide derivatives can be produced by reacting the quinoline-6-carboxylic ester derivative produced according to scheme 3 or 4 with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative in a suitable solvent, for example, 1,2-dichlorobenzene, or in a solvent-free system in the presence of a suitable base, for example, 4-dimethylaminopyridine (step (i)), subjecting the resultant compound to ester hydrolysis with a suitable alkali reagent, for

example, lithium hydroxide (step (ii)), and condensing the resultant carboxylic acid derivative with an amine using a suitable condensing agent, for example, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate (step (iii)).

[0147] The N-unsubstituted amide derivatives can be synthesized through the following two routes.

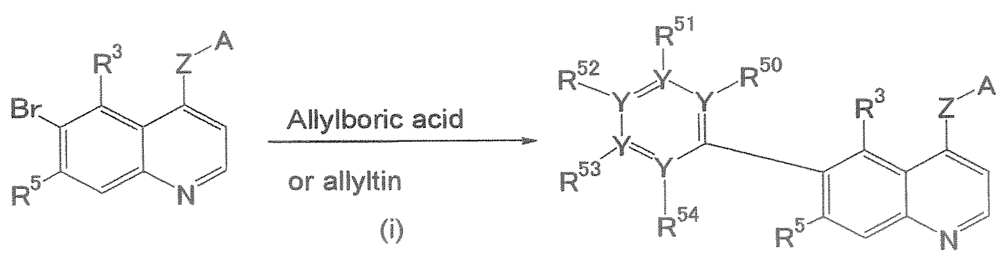
(I) The aimed compounds can be synthesized by reacting the compound produced in step (i) with ammonia (step (vi)).

(II) The aimed compounds can be synthesized by reacting the quinoline-6-carboxylic ester derivative with ammonia (step (iv)) and reacting the resultant compound with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative (step (v)) in a suitable solvent, for example, 1,2-dichlorobenzene, or in a solvent-free system, in the presence of a suitable base, for example, 4-dimethylaminopyridine.

[0148] Scheme 11

The 6-phenylquinoline derivatives according to the present invention can be produced, for example, according to scheme 11.

[Chemical formula 30]



wherein

R^{50} to R^{53} represent (i) hydroxyl, (ii) a halogen atom, (iii) cyano group, (iv) nitro group, (v) amino group wherein one or two hydrogen atoms in the amino group are optionally substituted by C1-4 alkyl, (vi) C1-4 alkyl, (vii) C2-4 alkenyl, (viii) C2-4 alkynyl, (ix) C1-4 alkoxy, (x) C1-4 alkylthio, (xi) -CO-OR^f, or (xii) -CO-NR^{g}R^h wherein R^f, R^g, and R^h, which

may be the same or different, represent a hydrogen atom or C1-4 alkyl, and

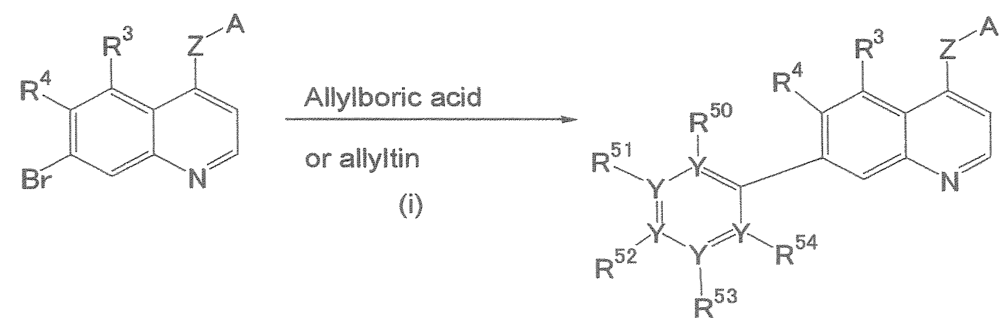
the other substituents are as defined above.

[0149] The aimed compounds can be produced by reacting the 6-bromoquinoline derivative produced according to scheme 3 or 4 with an alkyltin reagent or an alkylboric acid reagent in the presence of a suitable transition metal catalyst, for example, tetrakistriphenylphosphine palladium (step (i)).

[0150] Scheme 12

The 7-phenylquinoline derivatives according to the present invention can be produced, for example, according to scheme 12.

[Chemical formula 31]



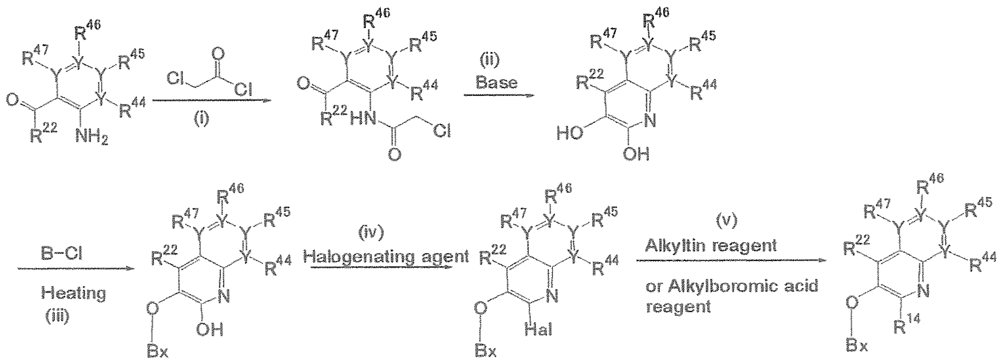
wherein the substituents are as defined above.

[0151] The aimed compounds can be produced by reacting the 7-bromoquinoline derivative produced according to scheme 3 or 4 with an alkyltin reagent or an alkylboric acid reagent in the presence of a suitable transition metal catalyst, for example, tetrakistriphenylphosphine palladium (step (i)).

[0152] Scheme 13

The 2-heteroring-naphthyridine derivatives according to the present invention can be produced, for example, according to scheme 13.

[Chemical formula 32]



wherein

Hal represents a halogen atom,

Bx represents the compound produced in schemes 3 to 10, and

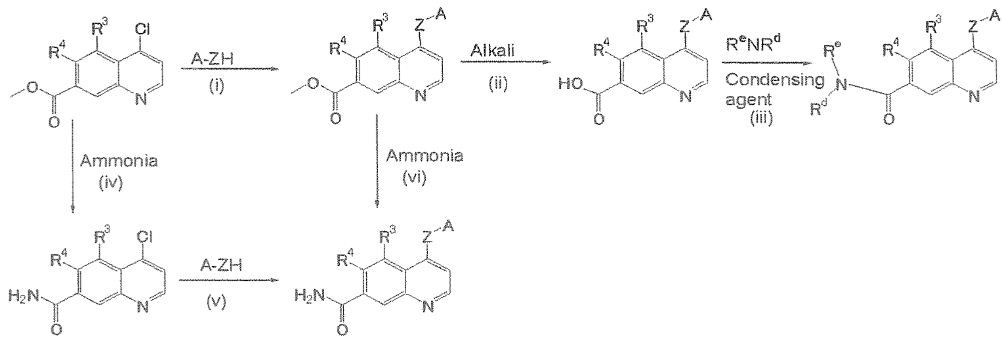
the other substituents are as defined above.

[0153] The aimed compounds can be produced by reacting an aniline derivative with chloroacetyl chloride (step (i)), then reacting the resultant amide derivative with a suitable base, for example, an aqueous potassium hydroxide solution (step (ii)) to give a 2,3-dihydroxypyridine derivative, reacting the 2,3-dihydroxypyridine derivative with the compound produced according to schemes 3 to 10 in a suitable solvent, for example, o-dichlorobenzene, or in a solvent-free system (step (iii)) to give a 2-hydroxyquinoline derivative, reacting the 2-hydroxyquinoline derivative with a suitable halogenating agent, for example, tetrabutylammonium bromide (step (iv)) to give a 2-haloquinoline derivative, and reacting the 2-haloquinoline derivative with an alkyltin reagent or an alkylboric acid reagent in the presence of a suitable transition metal catalyst, for example, tetrakistriphenylphosphine palladium (step (v)).

[0154] Scheme 14

The 7-amidoquinoline derivatives according to the present invention can be produced, for example, according to scheme 14.

[Chemical formula 33]



wherein the substituents are as defined above.]

[0155] The N-monosubstituted or N-disubstituted amide derivatives can be produced by reacting the quinoline-7-carboxylic ester derivative produced according to scheme 3 or 4 with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative in a suitable solvent, for example, 1,2-dichlorobenzene, or in a solvent-free system in the presence of a suitable base, for example, 4-dimethylaminopyridine (step (i)), subjecting the resultant compound to ester hydrolysis with a suitable alkali reagent, for example, lithium hydroxide (step (ii)), and condensing the resultant carboxylic acid derivative with an amine using a suitable condensing agent, for example, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate (step (iii)).

[0156] The N-unsubstituted amide derivatives can be synthesized through the following two routes.

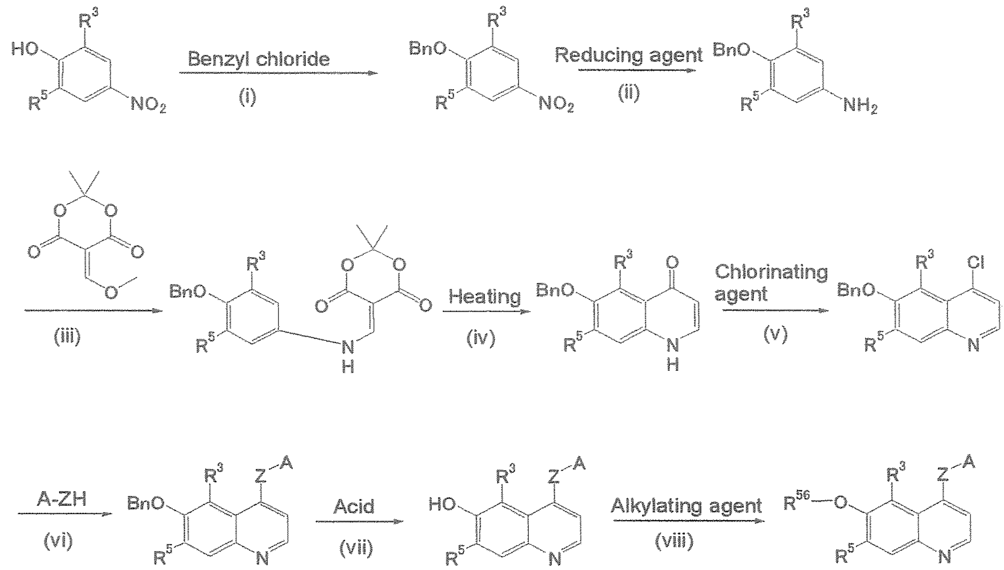
(I) The aimed compounds can be synthesized by reacting the compound produced in step (i) with ammonia (step (vi)).

(II) The aimed compounds can be synthesized by reacting the quinoline-7-carboxylic ester derivative with ammonia (step (iv)) and reacting the resultant compound with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative (step (v)) in a suitable solvent, for example, 1,2-dichlorobenzene, or in a solvent-free system, in the presence of a suitable base, for example, 4-dimethylaminopyridine.

[0157] Scheme 15

The 6-alkoxyquinoline derivatives or 7-alkoxyquinoline derivatives according to the present invention can be produced, for example, according to scheme 15.

[Chemical formula 34]



wherein

R^{56} represents a substituent that can be selected when $-OR^{56}$ is provided in the definition of R^4, and

the other substituents are as defined above.

[0158] The aimed 6-alkoxyquinoline derivatives can be produced by reacting a 4-nitrophenol derivative with benzyl chloride in a suitable solvent, for example, N,N-dimethylformamide, in the presence of a suitable base, for example, potassium carbonate (step (i)), treating the resultant compound in the same manner as shown in scheme 4 (steps (ii) to (vi)) to give a 6-benzyloxyquinoline derivative, treating the resultant 6-benzyloxyquinoline derivative with a suitable acid, for example, methanesulfonic acid/trifluoroacetic acid (step (vii)) to remove the benzyl group for deprotection, and reacting the phenol compound thus obtained with an alkylating agent in a suitable solvent, for example, N,N-dimethylformamide, in the presence of a suitable base, for example, potassium carbonate (step (viii)).

The aimed 7-alkoxyquinoline derivatives can be

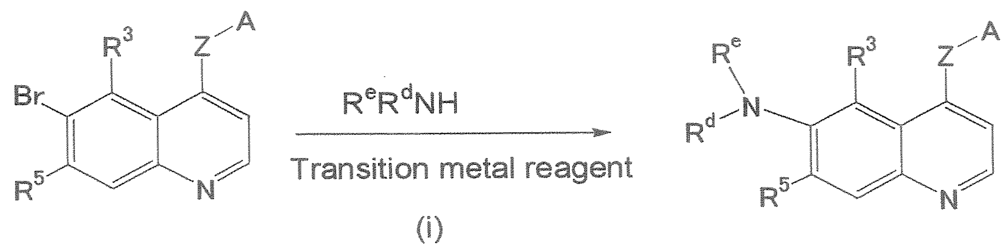
produced via the same steps as described above, except that a 3-nitrophenol derivative is used as the starting compound.

This scheme was described taking 6-alkoxyquinoline derivatives as an example. However, 7-alkoxyquinoline derivatives can also be produced likewise.

[0159] Scheme 16

The 6-alkylamine derivatives according to the present invention can be produced, for example, according to scheme 16.

[Chemical formula 35]



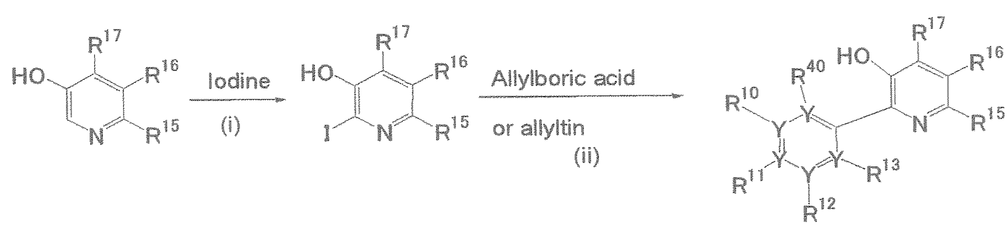
wherein the substituents are as defined above.

[0160] The aimed compounds can be produced by reacting the 6-bromoquinoline derivative produced according to scheme 3 or 4 with an alkylamine in the presence of a suitable transition metal catalyst, for example, palladium acetate, and a suitable base, for example, cesium carbonate (step (i)).

[0161] Scheme 17

The bipyridine derivatives as a partial structure of the compounds according to the present invention can be produced, for example, according to scheme 17.

[Chemical formula 36]



wherein the substituents are as defined above.

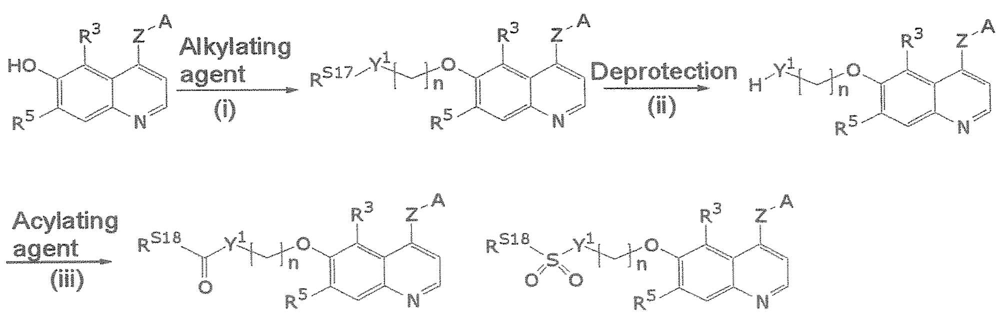
[0162] The aimed compounds can be produced by reacting

a 3-hydroxypyridine derivative with iodine in a suitable solvent, for example, methanol/water (step (i)) and then reacting the resultant compound with an alkyltin reagent or an alkylboric acid reagent in the presence of a suitable transition metal catalyst, for example, tetrakistriphenylphosphine palladium (step (ii)).

[0163] <u>Scheme 18</u>

The quinoline derivatives substituted at the 6-position by amide or by an ester derivative according to the present invention can be produced, for example, according to scheme 18.

[Chemical formula 37]



wherein the substituents are as defined above; Y^1 represents N or CH; and R^{s17} and R^{s18} represent C1-6 alkyl optionally substituted by amino.

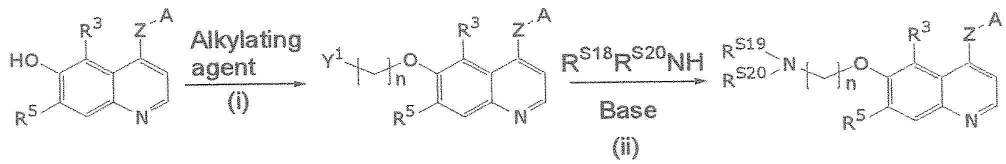
The aimed compounds can be produced by reacting a quinolin-6-ol derivative with an alkylating agent having a protected functional group, for example, n-(2-bromoethyl)phthalimide, in the presence of a base, for example, potassium carbonate (step (i)), deprotecting the resultant compound under suitable conditions, for example, with hydrazine (step (ii)), and reacting the produced functional group with an acylating agent, for example, acetic anhydride, in the presence of a suitable base, for example, triethylamine (step (iii)).

[0164] <u>Scheme 19</u>

The derivatives having alkylamine at the 6-position

according to the present invention can be produced, for example, according to scheme 19.

[Chemical formula 38]



wherein the substituents are as defined above and R^{s19} and R^{s20} represent C1-4 alkyl or phenyl.

The aimed compounds can be produced by reacting a quinolin-6-ol derivative with an alkyl dihalide, for example, 1-bromo-2chloro-ethane, in the presence of a base, for example, potassium carbonate (step (i)) and reacting the resultant compound with an amine in the presence of a suitable base, for example, potassium carbonate (step (ii)).

[0165] Use of compounds/pharmaceutical composition

The compounds according to the present invention can inhibit the action of TGFβ on cells in vitro (see Test Example 1A).

Likewise, the quinoline derivatives or quinazoline derivatives of Reference Examples (that is, compounds r1 to r469) having structures close to the compounds according to the present invention can also inhibit the action of TGFβ on cells in vitro (see Test Example 1B). Therefore, a person having ordinary skill in the art could easily understand that naphthyridine derivatives, thienopyridine derivatives, and thienopyrimidine derivatives (falling within the scope of the present invention), which have the same substituents as the quinoline derivatives or quinazoline derivatives of Reference Examples and are different from the quinoline derivatives or quinazoline derivatives of Reference Examples only in the ring structure of the mother nucleus, can also inhibit the action of TGFβ on cells in vitro.

[0166] As described in the column of BACKGROUND ART, the inhibition of TGFβ has been regarded as effective for the

prevention or treatment of all of diseases involving the fibrosis including chronic renal diseases. Examples of documents showing the correlation between TGFβ and these diseases are as described in the column of BACKGROUND ART.

[0167] The compounds according to the present invention actually exhibited anti-fibrotic activity in vivo (see Test Example 7).

Further, the quinoline derivatives or quinazoline derivatives of the Reference Examples actually exhibited anti-fibrotic activity in vivo (see Test Examples 2 to 4). Accordingly, it would be apparent, from these Test Examples, to a person having ordinary skill in the art that the compounds according to the present invention can be used for the prevention or treatment of diseases for which TGFβ inhibition is effective therapeutically.

[0168] Furthermore, the compounds according to the present invention actually suppressed cell growth inhibitory action in a test using A549 cells (Test Example 6). Furthermore, the compounds according to the present invention actually suppressed BMP signal inhibitory action in vitro (Test Example 7).

[0169] It was found that some of the compounds according to the present invention are superior to the conventional compounds having TGF-β inhibitory activity in an improvement in pharmacokinetic profile, an improvement in selectivity for various kinases, or a reduction in cell growth inhibitory activity. For example, the selectivity for BMP signals is included in the selectivity for various kinases. BMP signals are deeply involved in the differentiation of osteoblasts, and it has recently been suggested that the genetic mutation of receptors (ALK1 and BMP type II receptors) related to the signals is deeply involved in the onset of hereditary hemorrhagic telangiectasia and primary pulmonary hypertension (J Soc Biol. 2002; 196(1): 53-8). Further, compounds, which strongly inhibit cell growth, are considered to be related directly to the development of toxicity in individuals. For example, compounds 178, 179, 181,

182, 184, 186, 187, 192, 194, 200 to 202, 204 to 206, 217, 222 and 225 may be mentioned as compounds for which the above improvement has been made.

[0170] More specifically, compounds 179, 181, 182, 184, 186, 187 and 205 had reduced inhibitory activity against cell growth or BMP4 signals as compared with Example 261 or Example 269 described in WO 03/00660. Likewise, compounds 192, 194, 200, 201, 202, 204, 206, 217, 222 and 225 had reduced inhibitory activity against cell growth of A549 cells and reduced inhibitory activity against BMP4 signals as compared with Example 274 described in WO 03/00660.

[0171] Accordingly, the compounds according to the present invention can be used for the prevention or treatment of diseases for which TGFβ inhibition is effective therapeutically. Further, the compounds according to the present invention can be used for ex vivo expansion of cells.

[0172] The term "TGFβ inhibition" as used herein means the inhibition of the intracellular or tissue activity of TGFβ, a kind of cytokine.

According to the present invention, there is provided a method for preventing or treating a disease for which TGFβ inhibition is effective therapeutically or prophylactically, said method comprising the step of administering a therapeutically or prophylactically effective amount of a compound according to the present invention to a patient. The term "patient" as used herein means a patient requiring the treatment or prevention of the disease for which TGFβ inhibition is effective therapeutically or prophylactically.

According to the present invention, there is provided use of the compounds according to the present invention, for the manufacture of a medicament used in the treatment or prevention of diseases for which TGFβ inhibition is effective therapeutically or prophylactically.

[0173] According to the present invention, there is provided a pharmaceutical composition, comprising a compound according to the present invention or a pharmaceutically

acceptable salt or solvate thereof. The pharmaceutical composition according to the present invention can be used for the prevention or treatment of diseases for which TGFβ inhibition is effective therapeutically or prophylactically.

The disease for which TGFβ inhibition is effective therapeutically or prophylactically is preferably a disease involving organ or tissue fibrosis.

Further, diseases for which TGFβ inhibition is effective therapeutically or prophylactically include chronic renal disease, acute renal disease, hepatic fibrosis, cirrhosis, pulmonary fibrosis, scleroderma, wound healing, arthritis, congestive cardiac disease, ulcer, ocular disorder, corneal problem, diabetic nephropathy, peritoneal sclerosis, arteriosclerosis, peritoneal adhesions, and subdermal adhesion.

In another preferred embodiment of the present invention, the disease for which TGFβ inhibition is effective therapeutically or prophylactically is a malignant tumor.

[0174] In another preferred embodiment of the present invention, the compounds or pharmaceutical compositions according to the present invention can be used for ex vivo expansion of cells. The cells are preferably hematopoietic stem cells.

Accordingly, in a further preferred embodiment of the present invention, there is provided a method for ex vivo expansion of cells, comprising the step of adding a compound according to the present invention or a pharmaceutically acceptable salt or solvate thereof, in an amount effective for promoting cell growth, to intended cells in vitro to amplify the cells.

In another embodiment of the present invention, there is provided a promoter for ex vivo expansion of cells comprising a compound according to the present invention or a pharmaceutically acceptable salt or solvate thereof.

In still another embodiment of the present invention, there is provided a TGFβ inhibitor comprising a compound according to the present invention or a

pharmaceutically acceptable salt or solvate thereof.

[0175] The compounds according to the present invention can be administered to human and non-human animals orally or parenterally by administration routes, for example, intravenous administration, intramuscular administration, subcutaneous administration, rectal administration, or percutaneous administration.

Therefore, the pharmaceutical composition comprising a compound according to the present invention may be formulated into suitable dosage forms according to the administration routes. Specifically, oral preparations include tablets, capsules, powders, granules, and syrups, and parenteral preparations include injections, suppositories, tapes, and ointments.

These various preparations may be prepared by conventional methods, for example, with pharmaceutically acceptable carriers, that is, commonly used excipients, disintegrants, binders, lubricants, colorants, and diluents.

Excipients include, for example, lactose, glucose, corn starch, sorbit, and crystalline cellulose. Disintegrants include, for example, starch, sodium alginate, gelatin powder, calcium carbonate, calcium citrate, and dextrin. Binders include, for example, dimethylcellulose, polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, gum arabic, gelatin, hydroxypropylcellulose, and polyvinyl pyrrolidone. Lubricants include, for example, talc, magnesium stearate, polyethylene glycol, and hydrogenated vegetable oils.

In preparing the above injections, if necessary, for example, buffering agents, pH adjustors, stabilizers, tonicity adjusting agents, and preservatives may be added.

[0176] The content of a compound according to the present invention in the pharmaceutical composition according to the present invention may vary according to the dosage form. The content, however, is generally 0.5 to 50% by weight, preferably 1 to 20% by weight, based on the whole composition.

The dose may be appropriately determined in

consideration of particular conditions, for example, the age, weight, sex, type of disease, and severity of condition of patients. The preparation may be administered, for example, in an amount of 0.1 to 100 mg/kg, preferably 0.1 to 30 mg/kg. This dose may be administered at a time daily or divided doses of several times daily.

Compounds according to the present invention may be administered in combination with other medicaments, for example, carcinostatic agents. The adminstration can be carried out simultaneously or sequentially. The type, administration interval and the like of the carcinostatic agent can be determined by taking into consideration the type of cancer and the conditions of the patient.

[0177] When the compounds according to the present invention are used in the ex vivo expansion fo cells, a suitable medium may be selected or prepared depending upon the type of cells and the like. The amount of the compounds according to the present invention added to the medium may be properly determined depending, for example, upon the type and applications of the cells. The addition amount is preferably 0.01 to 50 μM, more preferably 0.1 to 20 μM.

In another embodiment of the present invention, there is provided a method for inhibiting the action of TGFβ on cells, comprising the step of applying an effective amount of a compound according to the present invention to cells present in vitro or in vivo.

[EXAMPLES]

[0178] The present invention is further illustrated by the following Examples. However, it should be noted that embodiments described in the Examples are not intended as a limitation of the invention.

[0179] The compounds according to the present invention were produced as follows.

The relationship between the produced compounds and schemes applied to the production of the compounds are

shown in the following table.

[0180]

Scheme	Compound
1	: Partial structure of compounds 1 to 51 Synthesis of partial structures of compounds 103 to 108, 110, 111, 117, 119 to 121, 126, 130, 131, 133, 136 to 146, 154 to 159 and 162 to 177
2	: Partial structure of compounds 52 to 100 Synthesis of partial structures of compounds 101, 102, 113, 114, 116, 118, 123 to 125, 127, 128, 132, 134, 135, 147 to 153, 160 and 161
3	: Compounds 1, 3, 13, 15, 37, 43 to 46, 49, 50, 52 to 54, 81 to 91, 93 to 98, 103, 111, 115, 117, 134, 135, 156, 157 and 188
4	: Compounds 2, 4, 14, 16, 55 to 63, 101, 102, 104, 105, 110, 114, 119, 130 to 133, 150, 158 to 162 and 170
5	: Compounds 28, 29, 71 and 72
6	: Compounds 23 to 27, 38, 39, 41, 48, 51, 68 to 70 and 100
7	: Compounds 32 to 35, 75 to 78 and 180
8	: Compounds 30, 73, 121 and 128
9	: Compounds 31 and 74
10	: Compounds 22, 65, 66, 99, 146, 148, 149, 152 and 153
11	: Compounds 5 to 12
12	: Compounds 17 to 21, 106 to 108, 155, 163 to 169 and 171 to 177
13	: Compound 92
14	: Compounds 113, 116, 126, 127, 145, 147, 151, 179, 185, 193, 194 and 217
15	: Compounds 118, 120, 123 to 125, 136 to 144, 178, 181, 183, 184, 186, 190 to 192, 200 to 202, 205, 210, 213 to 216, 222 and 225
16	: Compound 154
17	: Synthesis of partial structure of Compound 115
18	: Compounds 182, 187, 203, 204, 206 to 208 and

224

19 : Compounds 189, 209, 211, 212, 218 to 221 and 223

[0181] Example 1: 5,6-Dimethyl-3-(quinolin-4-yloxy)-[2,2']bipyridine (compound 1)

2,3-Dimethylfuran (5.0 g) was dissolved in diethyl ether (75 ml) under an argon atmosphere. A 1.6 M n-butyllithium/hexane solution (35.7 ml) was added dropwise to the solution at 0°C, and the mixture was stirred under reflux for 2.5 hr. The mixture was then cooled to -78°C, 2-cyanopyridine (6.0 g) dissolved in diethyl ether (20 ml) was added dropwise thereto, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was poured into ice to stop the reaction and was adjusted to pH 5 by the addition of 2 M hydrochloric acid, followed by extraction with chloroform. The chloroform layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-ethyl acetate system to give (4,5-dimethylfuran-2-yl)-(2-pyridyl)-methanone (1.8 g, yield 17%). (4,5-Dimethylfuran-2-yl)-(2-pyridyl)-methanone (1.6 g), methanol (15 ml), and a 28% aqueous ammonia solution (15 ml) were placed in a sealed tube, and the mixture was stirred at 160°C overnight. The reaction mixture was cooled to room temperature, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography with a hexane-ethyl acetate system to give 5,6-dimethyl-[2,2']bipyridinyl-3-ol (1.2 g, yield 75%).

[0182] Dimethyl sulfoxide (1.5 ml) was added to 5,6-dimethyl-[2,2']bipyridinyl-3-ol (30 mg), 4-chloroquinoline (74 mg), and cesium carbonate (147 mg), and the mixture was stirred at 130°C for 7 hr. The reaction mixture was cooled to room temperature, and water was added to the cooled mixture.

The mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with an ethyl acetate system to give the title compound (21 mg, yield 43%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.67 (s, 3H), 6.44 (d, J = 5.2 Hz, 1H), 7.10 (ddd, J = 7.6, 4.9, 1.0 Hz, 1H), 7.37 (s, 1H), 7.53 - 7.60 (m, 2H), 7.73 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 8.35 (dd, J = 8.3, 1.4 Hz, 1H), 8.48 - 8.53 (m, 1H), 7.57 (d, J = 5.2 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 328 $(M+1)^+$

[0183] Example 2: 3-(6-Bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 2)

Diphenyl ether (80 ml) was added to 4-bromoaniline (4.5 g) and 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxan-4,6-dione (5.4 g), and the mixture was stirred at 80°C for one hr. Biphenyl (24.2 g) was added thereto, and the mixture was stirred at 220°C for 3 hr. The reaction mixture was cooled to room temperature, and diethyl ether was added to the cooled mixture. The precipitated crystal was collected by filtration and was washed with diethyl ether. The residue was purified by column chromatography with a hexane-acetone system to give 6-bromoquinolone (1.57 g, yield 27%).

Thionyl chloride (5 ml) and a minor amount of dimethylformamide were added to 6-bromoquinolone (1.6 g), and the mixture was stirred under reflux for 3 hr. The reaction mixture was added to a saturated aqueous sodium bicarbonate solution under ice cooling, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a

hexane-ethyl acetate system to give 6-bromo-4-chloroquinoline (1.43 g, yield 85%).

[0184] Dimethylsulfoxide (25 ml) was added to 5,6-dimethyl-[2,2']bipyridinyl-3-ol (500 mg), 6-bromo-4-chloroquinoline (723 mg), cesium carbonate (2.4 g), and 4-dimethylaminopyridine (916 mg), and the mixture was stirred at 130°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to the cooled reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-acetone system to give the title compound (886 mg, yield 87%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.66 (s, 3H), 6.44 (d, J = 5.1 Hz, 1H), 7.11 (ddd, J = 7.6, 4.6, 1.0 Hz, 1H), 7.36 (s, 1H), 7.61 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.79 (dd, J = 8.8, 2.2 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 8.42 - 8.47 (m, 1H), 8.52 (d, J = 2.2 Hz, 1H), 8.55 (d, J = 5.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 406 $(M+1)^+$

[0185] Example 3: 5,6-Dimethyl-3-(6-trifluoromethyl-quinolin-4-yloxy)-[2,2']bipyridine (compound 3)

4-Chloro-6-trifluoromethylquinoline (50 mg), 5,6-dimethyl-[2,2']bipyridinyl-3-ol (43 mg), and 4-dimethylaminopyridine (79 mg) were dissolved in dimethylsulfoxide (1 ml). Cesium carbonate (211 mg) was added to the solution, and the mixture was stirred at 130°C overnight. The mixture was cooled to room temperature, an aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the organic layer was extracted with chloroform. The chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the

reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (77 mg, yield 89%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H), 2.68 (s, 3H), 6.57 (d, J = 5.6 Hz, 1H), 7.09 (ddd, J = 1.0, 4.9, 7.6 Hz, 1H), 7.41 (s, 1H), 7.63 (m, 1H), 7.95 - 7.97 (m, 2H), 8.28 (m, 2H), 8.67 (d, J = 5.4 Hz, 1H), 8.73 (s, 1H)

Mass spectrometric value (ESI-MS, m/z): 418 $(M+Na)^+$

[0186] Example 4: 3-(6-Methoxy-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 4)

4-Methoxyaniline (1.27 g) and 5-methoxymethylene-2,2-dimethyl-[1,3]dioxan-4,6-dione (1.82 g) were dissolved in 2-propanol (40 ml), and the solution was stirred at 50°C for 2 hr. The solvent was removed by distillation under the reduced pressure, and the residue was washed with ether to give 5-[(4-methoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxan-4,6-dione (1.98 g, yield 73%).

5-[(4-Methoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxan-4,6-dione (1.28 g) and biphenyl (5.2 g) were suspended in diphenyl ether (20 ml), and the suspension was stirred at 220°C for one hr. The reaction mixture as such was purified by column chromatography with a methanol-chloroform system to give 6-methoxy-1H-quinolin-4-one (398 mg, yield 49%).

6-Methoxy-1H-quinolin-4-one (398 mg) was suspended in diisopropylethylamine (3 ml), phosphorus oxychloride (1 ml) was added to the suspension, and the mixture was stirred at 100°C for one hr. Water was added to the reaction mixture under ice cooling, and the aqueous layer was neutralized with an aqueous sodium hydrogencarbonate solution. The organic layer was extracted with ethyl acetate, and the ethyl acetate layer was washed with water and was

dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an acetone-chloroform system to give 4-chloro-6-methoxyquinoline (375 mg, yield 42%).

[0187] 4-Chloro-6-methoxyquinoline (270 mg), 5,6-dimethyl-[2,2']bipyridinyl-3-ol (279 mg), and 4-dimethylaminopyridine (510 mg) were dissolved in dimethylsulfoxide (4 ml), cesium carbonate (1.36 g) was added to the solution, and the mixture was stirred at 130°C overnight. The mixture was cooled to room temperature, an aqueous sodium hydrogencarbonate solution was added to the reaction mixture, and the organic layer was extracted with chloroform. The chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (411 mg, yield 83%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.66 (s, 3H), 3.95 (s, 3H), 6.45 (dd, J = 0.7, 5.1 Hz, 1H), 7.11 (ddd, J = 1.2, 4.9, 7.6 Hz, 1H), 7.37 (s, 1H), 7.39 (m, 1H), 7.57 - 7.61 (m, 2H), 7.82 (dd, J = 1.0, 7.8 Hz, 1H), 7.99 (d, J = 9.3 Hz, 1H), 8.44 (d, J = 5.1 Hz, 1H), 8.50 (d, J = 4.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 380 $(M+Na)^+$

[0188] <u>Example 5: 5,6-Dimethyl-3-(6-phenyl-quinolin-4-yloxy)-[2,2']bipyridine (compound 5)</u>

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and phenylboric acid (27 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 3 hr. The reaction mixture was cooled to room temperature, and water was added to the cooled

mixture. The mixture was extracted with ethyl acetate, the ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-acetone system to give the title compound (31 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.67 (s, 3H), 6.47 (d, J = 5.1 Hz, 1H), 7.09 (ddd, J = 7.3, 4.9, 1.0 Hz, 1H), 7.37 - 7.43 (m, 2H), 7.50 (dd, J = 7.8, 7.8 Hz, 2H), 7.56 (ddd, J = 7.8, 7.8, 2.0 Hz, 1H), 7.76 (d, J = 7.3 Hz, 2H), 7.83 (d, J = 8.0 Hz, 1H), 8.01 (dd, J = 9.0, 2.2 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H), 8.48 - 8.51 (m, 1H), 8.54 - 8.59 (m, 2H)

Mass spectrometric value (ESI-MS, m/z): 404 $(M+1)^+$

[0189] Example 6: 5,6-Dimethyl-3-(6-pyridin-3-yl-quinolin-4-yloxy)-[2,2']bipyridine (compound 6)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 3-pyridylboric acid (18 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 3 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was

purified by column chromatography with a chloroform-acetone system to give the title compound (30 mg, yield 100%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.67 (s, 3H), 6.49 (d, J = 5.4 Hz, 1H), 7.09 (ddd, J = 7.6, 4.9, 1.0 Hz, 1H), 7.38 - 7.46 (m, 2H), 7.59 (ddd, J = 7.8, 7.8, 2.0 Hz, 1H), 7.85 (ddd, J = 8.0, 1.2, 1.2 Hz, 1H), 7.98 (dd, J = 8.8, 2.2 Hz, 1H), 8.02 - 8.07 (m, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.43 - 8.47 (m, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.60 (d, J = 5.1 Hz, 1H), 8.65 (dd, J = 4.9, 1.7 Hz, 1H), 9.00 (d, J = 1.7 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 427 $(M+Na)^+$

[0190] <u>Example 7: 5,6-Dimethyl-3-(6-pyridin-4-yl-quinolin-4-yloxy)-[2,2′]bipyridine (compound 7)</u>

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (30 mg) and tetrakistriphenylphosphine palladium (9 mg) and 4-pyridylboric acid (18 mg) under an argon atmosphere, and the mixture was stirred at 70°C overnight. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-acetone system to give the title compound (16 mg, yield 55%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.67 (s, 3H), 6.49 (d, J = 5.4 Hz, 1H), 7.09 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.41 (s, 1H), 7.59 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.68 (dd, J = 4.6, 1.7 Hz, 2H), 7.86 (d, J = 8.0 Hz, 1H), 8.02 (dd, J = 8.8, 2.2 Hz,

1H), 8.16 (d, J = 8.8 Hz, 1H), 8.40 - 8.45 (m, 1H), 8.61 (d, J = 5.1 Hz, 1H), 8.66 (d, J = 2.2 Hz, 1H), 8.73 (dd, J = 6.4, 1.7 Hz, 2H)
Mass spectrometric value (ESI-MS, m/z): 405 $(M+1)^+$

[0191] Example 8: 5,6-Dimethyl-3-(6-p-tolyl-quinolin-4-yloxy)-[2,2']bipyridine (compound 8)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 4-methylphenylboric acid (30 mg) under an argon atmosphere and the mixture was stirred at 70°C for 3 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-acetone system to give the title compound (31 mg, yield 100%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.43 (s, 3H), 2.67 (s, 3H), 6.46 (d, J = 5.1 Hz, 1H), 7.09 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 7.39 (s, 1H), 7.56 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 7.8 Hz, 1H), 8.00 (dd, J = 8.8, 2.0 Hz, 1H), 8.10 (d, J = 8.8 Hz, 1H), 8.49 - 8.54 (m, 2H), 8.55 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 418 $(M+1)^+$

[0192] Example 9: 2-[4-(5,6-Dimethyl-[2,2']bipyridin-3-yloxy)-quinolin-6-yl]-phen

ylamine (compound 9)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 2-aminophenylboric acid (30 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 3 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-acetone system to give the title compound (31 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.66 (s, 3H), 3.83 (brs, 2H), 6.47 (d, J = 5.1 Hz, 1H), 6.82 (dd, J = 8.0, 1.0 Hz, 1H), 6.88 (ddd, J = 8.6, 8.6, 1.2 Hz, 1H), 7.08 - 7.13 (m, 1H), 7.18 - 7.26 (m, 2H), 7.37 (s, 1H), 7.57 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.82 (ddd, J = 8.1, 8.1, 1.2 Hz, 1H), 7.87 (dd, J = 8.8, 2.0 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H), 8.43 (d, J = 2.0 Hz, 1H), 8.49 - 8.52 (m, 1H), 8.59 (d, J = 5.2 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 441 $(M+Na)^+$

[0193] Example 10: 3-[4-(5,6-Dimethyl-[2,2']bipyridin-3-yloxy)-quinolin-6-yl]-phenylamine (compound 10)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 3-aminophenylboric acid monohydrate (34 mg) under an argon

atmosphere, and the mixture was stirred at 70°C overnight. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate, and the ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-acetone system to give the title compound (31 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.67 (s, 3H), 3.80 (brs, 2H), 6.45 (d, J = 5.1 Hz, 1H), 6.70 - 6.76 (m, 1H), 7.02 - 7.17 (m, 3H), 7.26 - 7.31 (m, 1H), 7.38 (s, 1H), 7.57 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 8.8, 2.0 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.47 - 8.54 (m, 2H), 8.56 (d, J = 5.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 441 $(M+Na)^+$

[0194] Example 11: 3-[4-(5,6-Dimethyl-[2,2']bipyridin-3-yloxy)-quinolin-6-yl]-phenol (compound 11)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg) and 3-hydroxyphenylboric acid (31 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 3 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl

acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-acetone system to give the title compound (31 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.33 (s, 3H), 2.61 (s, 3H), 6.40 (d, J = 5.1 Hz, 1H), 6.77 - 6.84 (m, 1H), 7.06 (ddd, J = 7.6, 4.9, 1.0 Hz, 1H), 7.18 - 7.34 (m, 4H), 7.55 (ddd, J = 7.8, 7.8, 2.0 Hz, 1H), 7.79 (ddd, J = 8.0, 1.0, 1.0 Hz, 1H), 7.93 (dd, J = 9.0, 2.2 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.42 - 8.47 (m, 1H), 8.53 (d, J = 5.4 Hz, 1H), 8.57 (d, J = 2.2 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 420 $(M+1)^+$

[0195] Example 12: 4-[4-(5,6-Dimethyl-[2,2']bipyridin-3-yloxy)-quinolin-6-yl]-phenol (compound 12)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 4-hydroxyphenylboric acid (31 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 3 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-acetone system to give the title compound (31 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H), 2.65 (s, 3H), 6.46 (d,

J = 5.1 Hz, 1H), 6.95 (d, J = 8.5 Hz, 2H), 7.11 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.39 (s, 1H), 7.54 - 7.64 (m, 3H), 7.85 (d, J = 8.1 Hz, 1H), 7.95 (dd, J = 8.8, 2.0 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.48 - 8.51 (m, 2H), 8.54 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 420 $(M+1)^+$

[0196] Example 13: 3-(7-Chloro-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 13)

Dimethylsulfoxide (2.5 ml) was added to 5,6-dimethyl-[2,2′]bipyridinyl-3-ol (50 mg), 4,7-dichloroquinoline (99 mg), and cesium carbonate (244 mg), and the mixture was stirred at 130°C for 3 hr. 4,7-Dichloroquinoline (99 mg) was further added thereto, and the mixture was stirred at 130°C for 3 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a hexane-acetone system to give the title compound (80 mg, yield 88%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.66 (s, 3H), 6.41 (d, J = 5.1 Hz, 1H), 7.09 (ddd, J = 7.3, 4.6, 1.0 Hz, 1H), 7.38 (s, 1H), 7.51 (dd, J = 9.0, 2.2 Hz, 1H), 7.58 (ddd, J = 8.0, 8.0, 2.0 Hz, 1H), 7.82 (ddd, J = 8.1, 1.0, 1.0 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H), 8.29 (d, J = 8.8 Hz, 1H), 8.40 - 8.45 (m, 1H), 8.55 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 362 $(M+1)^+$

[0197] Example 14: 3-(7-Bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 14)

2-Propanol (90 ml) was added to 3-bromoaniline (5.0 g), and 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxan-4,6-dione (6.0

g) was added to the mixture with stirring at 70°C, and the mixture was stirred at 70°C for 3 hr. The reaction mixture was cooled to room temperature, and the precipitated crystal was collected by filtration and was washed with diethyl ether. The crude crystal thus obtained as such was used in the next reaction without purification.

Biphenyl (26.2 g) and diphenyl ether (75 ml) were added to the crude crystal, and the mixture was stirred at 230°C for one hr. The reaction mixture was cooled to room temperature, and ether was added to the cooled mixture. The precipitated crystal was collected by filtration and was washed with diethyl ether, and the crude crystal thus obtained as such was used in the next reaction without purification.

Thionyl chloride (15 ml) and a minor amount of dimethylformamide were added to the crude crystal, and the mixture was stirred under reflux for 3 hr. The reaction mixture was added to a saturated aqueous sodium bicarbonate solution under ice cooling, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-ethyl acetate system to give 7-bromo-4-chloroquinoline (2.40 g, yield 42%).

[0198] Dimethylsulfoxide (25 ml) was added to 5,6-dimethyl-[2,2']bipyridinyl-3-ol (500 mg), 7-bromo-4-chloroquinoline (723 mg), cesium carbonate (2.4 g), and 4-dimethylaminopyridine (916 mg), and the mixture was stirred at 130°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-acetone system to give the title compound (705 mg, yield 70%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.66 (s, 3H), 6.43 (d, J = 5.1 Hz, 1H), 7.09 (dd, J = 7.6, 4.6 Hz, 1H), 7.38 (s, 1H), 7.58 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.64 (dd, J = 9.0, 1.7 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 8.20 - 8.25 (m, 2H), 8.41 - 8.45 (m, 1H), 8.55 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 406 $(M+1)^+$

[0199] Example 15: 5,6-Dimethyl-3-(7-trifluoromethyl-quinolin-4-yloxy)-[2,2′]bipyridine (compound 15)

Dimethylsulfoxide (2.5 ml) was added to 5,6-dimethyl-[2,2′]bipyridinyl-3-ol (50 mg), 4-chloro-7-trifluoromethylquinoline (116 mg), and cesium carbonate (244 mg), and the mixture was stirred at 130°C for 3 hr. 4-Chloro-7-trifluoromethylquinoline (116 mg) was further added, and the mixture was stirred at 130°C for 3 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a hexane-acetone system to give the title compound (98 mg, yield 99%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.67 (s, 3H), 6.52 (d, J = 5.4 Hz, 1H), 7.09 (ddd, J = 7.4, 4.7, 1.1 Hz, 1H), 7.40 (s, 1H), 7.60 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.73 (dd, J = 8.8, 1.7 Hz, 1H), 7.86 (ddd, J = 7.8, 1.0, 1.0 Hz, 1H), 8.35 (s, 1H), 8.37 - 8.41 (m, 1H), 8.49 (d, J = 8.8 Hz, 1H), 8.65 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 396 $(M+1)^+$

[0200] Example 16: 3-(7-Methoxy-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 16)

3-Methoxyaniline (1.23 g) and

5-methoxymethylene-2,2-dimethyl-[1,3]dioxan-4,6-dione (1.90 g) were dissolved in 2-propanol (40 ml), and the mixture was stirred at 70°C for one hr. The solvent was removed by distillation under the reduced pressure, and the residue was washed with ether to give 5-[(3-methoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxan-4,6-dione (1.22 g, yield 44%).

5-[(3-Methoxy-phenylamino)-methylene]-2,2-dimethyl-[1,3]dioxan-4,6-dione (1.22 g) and biphenyl (5.1 g) were suspended in diphenyl ether (15 ml), and the mixture was stirred at 220°C for 1.5 hr. The reaction mixture as such was purified by column chromatography with a methanol-chloroform system to give 7-methoxy-1H-quinolin-4-one (394 mg, yield 51%).

7-Methoxy-1H-quinolin-4-one (394 mg) was suspended in diisopropylethylamine (3 ml), phosphorus oxychloride (1 ml) was added to the suspension, and the mixture was stirred at 100°C for one hr. Water was added to the reaction mixture under ice cooling. The aqueous layer was neutralized with an aqueous sodium hydrogencarbonate solution, and the organic layer was extracted with ethyl acetate. The ethyl acetate layer was then washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an acetone-chloroform system to give 4-chloro-7-methoxyquinoline (312 mg, yield 72%).

[0201] 4-Chloro-7-methoxyquinoline (170 mg), 5,6-dimethyl-[2,2']bipyridinyl-3-ol (176 mg), and 4-dimethylaminopyridine (322 mg) were dissolved in dimethylsulfoxide (2 ml). Cesium carbonate (860 mg) was added to the solution, and the mixture was stirred at 130°C overnight. The mixture was cooled to room temperature. An aqueous sodium hydrogencarbonate solution was added to the reaction mixture. The organic layer was extracted with chloroform, and the chloroform layer was then washed with

water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (273 mg, yield 87%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.66 (s, 3H), 3.96 (d, J = 1.2 Hz, 3H), 6.34 (dd, J = 2.2, 5.4 Hz, 1H), 7.10 (m, 1H), 7.21 (m, 1H), 7.36 (s, 1H), 7.40 (m, 1H), 7.57 (m, 1H), 7.81 (dd, J = 1.2, 8.1 Hz, 1H), 8.23 (dd, J = 1.5, 9.3 Hz, 1H), 8.48 - 8.49 (m, 2H)

Mass spectrometric value (ESI-MS, m/z): 380 $(M+Na)^+$

[0202] Example 17: 5,6-Dimethyl-3-(7-phenyl-quinolin-4-yloxy)-[2,2']bipyridine (compound 17)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(7-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and phenylboric acid (27 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-methanol system to give the title compound (30 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.67 (s, 3H), 6.44 (d, J = 5.2 Hz, 1H), 7.10 (ddd, J = 7.3, 4.6, 1.0 Hz, 1H), 7.39 - 7.45 (m, 2H), 7.51 (dd, J = 7.8, 7.8 Hz, 2H), 7.58 (ddd, J = 7.8,

7.8, 1.7 Hz, 1H), 7.75 - 7.79 (m, 2H), 7.82 - 7.87 (m, 2H), 8.27 (d, J = 1.7 Hz, 1H), 8.41 (d, J = 8.6 Hz, 1H), 8.50 - 8.53 (m, 1H), 8.59 (d, J = 5.4 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 426 $(M+Na)^+$

[0203] Example 18: 5,6-Dimethyl-3-(7-pyridin-3-yl-quinolin-4-yloxy)-[2,2′]bipyridine (compound 18)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(7-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 3-pyridylboric acid (18 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-methanol system to give the title compound (30 mg, yield 100%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.68 (s, 3H), 6.47 (d, J = 5.1 Hz, 1H), 7.10 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.40 (s, 1H), 7.44 (ddd, J = 7.8, 4.9, 0.7 Hz, 1H), 7.59 (ddd, J = 8.1, 8.1, 2.0 Hz, 1H), 7.81 (dd, J = 8.8, 2.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 8.05 (dd, J = 8.0, 2.4 Hz, 1H), 8.27 (d, J = 1.5 Hz, 1H), 8.45 - 8.50 (m, 2H), 8.61 (d, J = 5.4 Hz, 1H), 8.67 (dd, J = 4.9, 1.7 Hz, 1H), 9.03 (d, J = 1.5 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 427 $(M+Na)^+$

[0204] Example 19: 5,6-Dimethyl-3-(7-pyridin-4-yl-quinolin-4-yloxy)-[2,2′]bipyridin

e (compound 19)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(7-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 4-pyridylboric acid (18 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-methanol system to give the title compound (13 mg, yield 43%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.68 (s, 3H), 6.48 (d, J = 5.1 Hz, 1H), 7.10 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.41 (s, 1H), 7.60 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.68 (dd, J = 4.6, 1.7 Hz, 2H), 7.82 - 7.88 (m, 2H), 8.34 (d, J = 2.0 Hz, 1H), 8.45 - 8.50 (m, 2H), 8.62 (d, J = 5.2 Hz, 1H), 8.74 (dd, J = 4.6, 1.7 Hz, 2H)

Mass spectrometric value (ESI-MS, m/z): 427 $(M+Na)^+$

[0205] Example 20: 5,6-Dimethyl-3-(7-p-tolyl-quinolin-4-yloxy)-[2,2']bipyridine (compound 20)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(7-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 4-methylphenylboric acid (30 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to

the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-methanol system to give the title compound (31 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.43 (s, 3H), 2.67 (s, 3H), 6.42 (d, J = 5.1 Hz, 1H), 7.10 (ddd, J = 7.6, 4.9, 1.0 Hz, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.38 (s, 1H), 7.58 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.80 - 7.86 (m, 2H), 8.25 (d, J = 1.5 Hz, 1H), 8.39 (d, J = 8.8 Hz, 1H), 8.50 - 8.54 (m, 1H), 8.58 (d, J = 5.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 440 $(M+Na)^+$

[0206] Example 21: 3-[4-(5,6-Dimethyl-[2,2']bipyridin-3-yloxy)-quinolin-7-yl]-phenylamine (compound 21)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(7-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 3-aminophenylboric acid monohydrate (34 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The

solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-methanol system to give the title compound (31 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.67 (s, 3H), 3.81(brs, 2H), 6.43 (d, J = 5.1 Hz, 1H), 6.74 (ddd, J = 8.0, 2.2, 1.0 Hz, 1H), 7.05 - 7.18 (m, 3H), 7.29 (dd, J = 8.1, 8.1 Hz, 1H), 7.38 (s, 1H), 7.58 (ddd, J = 7.8, 7.8, 2.0 Hz, 1H), 7.80 (dd, J = 8.8, 2.0 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 8.23 (d, J = 1.7 Hz, 1H), 8.37 (d, J = 8.6 Hz, 1H), 8.50 - 8.54 (m, 1H), 8.58 (d, J = 5.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 441 $(M+Na)^+$

[0207] <u>Example 22: 4-(5,6-Dimethyl-[2,2']bipyridin-3-yloxy)-7-methoxy-quinoline-6-carboxylic acid amide (compound 22)</u>

Methyl 4-amino-2-methoxy-benzoate (1.07 g) and 5-methoxymethylene-2,2-dimethyl-[1,3]dioxan-4,6-dione (1.0 g) were dissolved in 2-propanol (20 ml), and the mixture was stirred at 70°C for one hr. The solvent was removed by distillation under the reduced pressure, and the residue was washed with ether to give methyl 4-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-2-methoxy-benzoate (1.71 g, yield 95%).

Methyl 4-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-2-methoxy-benzoate (1.70 g) and biphenyl (4.76 g) were suspended in diphenyl ether (15 ml), and the suspension was stirred at 240°C for one hr. The suspension was cooled to room temperature, and the precipitated crystal was collected by filtration and was washed with ether. The crystal thus obtained as such was used in the next reaction without further purification.

N,N-Dimethylformamide (2 drops) was added to the crystal thus obtained. Further, phosphorus oxychloride (2.5 ml) was added thereto, and the mixture was stirred at 100°C for 2

hr. The solvent was removed by distillation under the reduced pressure, and water was added to the residue under ice cooling. The aqueous layer was neutralized with an aqueous sodium hydrogencarbonate solution, and the organic layer was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give methyl 4-chloro-7-methoxy-quinoline-6-carboxylate (707 mg, yield 55%) (2 steps).

[0208] Methyl 4-chloro-7-methoxy-quinoline-6-carboxylate (120 mg) was dissolved in methanol (6 ml), 28% aqueous ammonia (6 ml) was added thereto, and the mixture was stirred at 40°C overnight. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give 4-chloro-7-methoxy-quinoline-6-carboxylic acid amide (91 mg, yield 80%).

4-Chloro-7-methoxy-quinoline-6-carboxylic acid amide (91 mg), 5,6-dimethyl-[2,2′]bipyridinyl-3-ol (115 mg), and 4-dimethylaminopyridine (141 mg) were dissolved in dimethylsulfoxide (3 ml), cesium carbonate (375 mg) was added to the solution, and the mixture was stirred overnight at 130°C. The mixture was cooled to room temperature, and water was added to the reaction mixture. The organic layer was extracted with chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (33 mg, yield 22%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.67 (s, 3H), 4.13 (s, 3H), 5.92 (m, 1H), 6.39 (d, J = 5.4 Hz, 1H), 7.08 (ddd, J = 1.2, 4.9, 7.6 Hz, 1H), 7.36 (s, 1H), 7.56 - 7.63 (m, 2H), 7.76 (m, 1H), 7.90 (m, 1H), 8.40 (m, 1H), 8.54 (d, J = 5.6 Hz, 1H), 9.27

temperature, and the cooled reaction mixture as such was applied to column chromatography with a methanol-chloroform system. The crude product as such was used in the next reaction without further purification.

The crude product was suspended in diisopropylethylamine (3 ml), phosphorus oxychloride (0.5 ml) was added to the suspension, and the mixture was stirred at 120°C for 3 hr. Water was added to the reaction mixture under ice cooling. The aqueous layer was neutralized with an aqueous sodium hydrogencarbonate solution, and the organic layer was extracted with ethyl acetate. The ethyl acetate layer was then washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an ethyl acetate-hexane system to give 6-benzyloxy-4-chloro-quinoline (147 mg, yield 10%) (3 steps).

[0347] 6-Benzyloxy-4-chloro-quinoline (147 mg), 5,6-dimethyl-[2,2′]bipyridinyl-3-ol (140 mg), and 4-dimethylaminopyridine (200 mg) were dissolved in dimethylsulfoxide (3 ml), cesium carbonate (540 mg) was added to the solution, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The organic layer was extracted with chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an acetone-chloroform system to give the title compound (158 mg, yield 66%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.66 (s, 3H), 5.21 (s, 2H), 6.43 (d, J = 5.1 Hz, 1H), 7.10 (ddd, J = 1.2, 4.9, 7.6 Hz, 1H), 7.35 - 7.55 (m, 8H), 7.67 (d, J = 2.7 Hz, 1H), 7.76 (m, 1H), 7.96 (d, J = 9.3 Hz, 1H), 8.44 (d, J = 5.1 Hz, 1H), 8.51 (m, 1H)

Mass spectrometric value (ESI-MS, m/z): 456 $(M+Na)^+$

[0348] Example 137: 3-(7-Benzyloxy-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 137)

3-Benzyloxy-aniline (1.0 g) and 5-methoxymethylene-2,2-dimethyl-[1,3]dioxan-4,6-dione (1.03 g) were suspended in 2-propanol (15 ml) and the suspension was stirred at 70°C for 3 hr. The reaction mixture was cooled to room temperature, was filtered, and was washed with ether. The residue as such was used in the next reaction without purification.

The residue and biphenyl (4.34 g) were suspended in diphenyl ether (12 ml), and the suspension was stirred at 240°C overnight. The reaction mixture was cooled to room temperature, and the cooled reaction mixture as such was applied to column chromatography with a methanol-chloroform system. The crude product as such was used in the next reaction without further purification.

The crude product was suspended in diisopropylethylamine (7 ml), phosphorus oxychloride (1.5 ml) was added to the suspension, and the mixture was stirred at 120°C for 30 min. Water was added to the reaction mixture under ice cooling. The aqueous layer was neutralized with an aqueous sodium hydrogencarbonate solution, and the organic layer was extracted with ethyl acetate. The ethyl acetate layer was then washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an ethyl acetate-hexane system to give 7-benzyloxy-4-chloro-quinoline (222 mg, yield 16%) (3 steps).

[0349] 7-Benzyloxy-4-chloro-quinoline (222 mg), 5,6-dimethyl-[2,2']bipyridinyl-3-ol (220 mg), and 4-dimethylaminopyridine (302 mg) were dissolved in dimethylsulfoxide (3 ml), cesium carbonate (820 mg) was added to the solution, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The organic layer was extracted with

chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an acetone-chloroform system to give the title compound (239 mg, yield 67%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H), 2.66 (s, 3H), 5.21 (s, 2H), 6.32 (d, J = 5.1 Hz, 1H), 7.10 (ddd, J = 1.2, 4.9, 7.6 Hz, 1H), 7.26 - 7.59 (m, 9H), 7.80 (d, J = 7.9 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.48 (d, J = 5.1 Hz, 1H), 8.52 (m, 1H)

Mass spectrometric value (ESI-MS, m/z): 456 $(M+Na)^+$

[0350] <u>Example 138: 3-(6-Benzyloxy-7-methoxy-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 138)</u>

6-Benzyloxy-4-chloro-7-methoxyquinoline (200 mg), 5,6-dimethyl-[2,2′]bipyridinyl-3-ol (195 mg), and 4-dimethylaminopyridine (244 mg) were dissolved in dimethylsulfoxide (3 ml), cesium carbonate (655 mg) was added to the solution, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The organic layer was extracted with chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an acetone-chloroform system to give the title compound (239 mg, yield 77%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 3H), 2.66 (s, 3H), 4.03 (s, 3H), 5.29 (s, 2H), 6.33 (d, J = 5.4 Hz, 1H), 7.08 (m, 1H), 7.30 - 7.39 (m, 5H), 7.47 (ddd, J = 2.0, 7.8, 7.8 Hz, 1H), 7.50 (m, 2H), 7.60 (s, 1H), 7.68 (d, J = 7.8 Hz, 1H), 8.38 (d, J = 5.4 Hz, 1H), 8.51 (m, 1H)

Mass spectrometric value (ESI-MS, m/z): 486 $(M+Na)^+$

[0351] <u>Example 139:</u>

4-(5,6-Dimethyl-[2,2']bipyridinyl-3-yloxy)-quinolin-6-ol (compound 139)

3-(6-Benzyloxy-quinolin-4-yloxy)-5,6-dimethyl-[2,2']-bipyridine (compound 136) (150 mg) was dissolved in trifluoroacetic acid (3 ml). Methanesulfonic acid (0.3 ml) was added to the solution, and the mixture was stirred at room temperature for one hr. Water was added to the reaction mixture, the mixture was neutralized with an aqueous sodium hydrogencarbonate solution, and the organic layer was extracted with chloroform. The chloroform layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a methanol-chloroform system to give the title compound (117 mg, yield 99%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.24 (s, 3H), 2.62 (s, 3H), 6.50 (d, J = 5.2 Hz, 1H), 7.13 (ddd, J = 1.2, 4.9, 7.9 Hz, 1H), 7.15 (s, 1H), 7.32 (m, 1H), 7.36 (dd, J = 2.8, 9.0 Hz, 1H), 7.51 (m, 1H), 7.66 (dd, J = 1.2, 8.0 Hz, 1H), 7.94 (d, J = 9.0 Hz, 1H), 8.45 (d, J = 5.2 Hz, 1H), 8.56 (m, 1H)

Mass spectrometric value (ESI-MS, m/z): 366 $(M+Na)^+$

[0352] Example 140: 4-(5,6-Dimethyl-[2,2']bipyridinyl-3-yloxy)-quinolin-7-ol (compound 140)

3-(7-Benzyloxy-quinolin-4-yloxy)-5,6-dimethyl-[2,2'] bipyridine (compound 137) (230 mg) was dissolved in trifluoroacetic acid (3 ml). Methanesulfonic acid (0.3 ml) was added to the solution, and the mixture was stirred at room temperature for one hr. Water was added to the reaction mixture, the mixture was neutralized with an aqueous sodium hydrogencarbonate solution, and the organic layer was extracted with chloroform. The chloroform layer was washed with water and was dried over anhydrous sodium sulfate. The

solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (182 mg, yield 100%).

^1H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.64 (s, 3H), 6.27 (d, J = 5.4 Hz, 1H), 6.87 (dd, J = 2.2, 9.0 Hz, 1H), 7.08 (dd, J = 4.9, 7.6 Hz, 1H), 7.23 (m, 1H), 7.40 (s, 1H), 7.58 (dd, J = 7.6, 7.8 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.99 (d, J = 9.0 Hz, 1H), 8.35 (d, J = 5.4 Hz, 1H), 8.50 (m, 1H)

Mass spectrometric value (ESI-MS, m/z): 344 $(M+1)^+$

[0353] Example 141: 4-(5,6-Dimethyl-[2,2′]bipyridinyl-3-yloxy)-7-methoxy-quinolin-6-ol (compound 141)

3-(6-Benzyloxy-7-methoxy-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 138) (230 mg) was dissolved in trifluoroacetic acid (3 ml). Methanesulfonic acid (0.3 ml) was added to the solution, and the mixture was stirred at room temperature for one hr. Water was added to the reaction mixture, the mixture was neutralized with an aqueous sodium hydrogencarbonate solution, and the organic layer was extracted with chloroform. The chloroform layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a methanol-chloroform system to give the title compound (106 mg, yield 55%).

^1H-NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 3H), 2.66 (s, 3H), 4.05 (s, 3H), 6.34 (d, J = 5.4 Hz, 1H), 7.11 (ddd, J = 1.2, 4.9, 7.6 Hz, 1H), 7.32 (s, 1H), 7.38 (s, 1H), 7.56 (ddd, J = 1.7, 7.8, 7.8 Hz, 1H), 7.68 (s, 1H), 7.79 (ddd, J = 1.0, 1.2, 7.8 Hz, 1H), 8.37 (d, J = 5.1 Hz, 1H), 8.57 (m, 1H)

Mass spectrometric value (ESI-MS, m/z): 374 $(M+1)^+$

[0354] Example 142:

2-[4-(5,6-Dimethyl-[2,2']bipyridinyl-3-yloxy)-quinolin-6-yloxy]-ethanol (compound 142)

4-(5,6-Dimethyl-[2,2']bipyridinyl-3-yloxy)-quinolin-6-ol (compound 139) (88 mg) was dissolved in N,N-dimethylformamide (3 ml). Potassium carbonate (200 mg) and 2-bromoethanol (0.2 ml) were added to the solution, and the mixture was stirred at 70°C overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a methanol-chloroform system to give the title compound (41 mg, yield 41%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H), 2.65 (s, 3H), 4.30 (t, J = 4.2 Hz, 2H), 4.23 (t, J = 4.4 Hz, 2H), 6.44 (d, J = 5.2 Hz, 1H), 7.11 (dd, J = 4.9, 7.6 Hz, 1H), 7.34 (s, 1H), 7.37 (m, 1H), 7.57 - 7.61 (m, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 8.45 (d, J = 5.1 Hz, 1H), 8.49 (m, 1H)

Mass spectrometric value (ESI-MS, m/z): 410 $(M+Na)^+$

[0355] Example 143: 2-[4-(5,6-Dimethyl-[2,2']bipyridinyl-3-yloxy)-quinolin-7-yloxy]-ethanol (compound 143)

4-(5,6-Dimethyl-[2,2']bipyridinyl-3-yloxy)-quinolin-7-ol (compound 140) (152 mg) was dissolved in N,N-dimethylformamide (3 ml). Potassium carbonate (200 mg) and 2-bromoethanol (0.2 ml) were added to the solution, and the mixture was stirred at 70°C overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer

chromatography with a methanol-chloroform system to give the title compound (93 mg, yield 54%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.66 (s, 3H), 4.05 (t, J = 4.2 Hz, 2H), 4.24 (t, J = 4.4 Hz, 2H), 6.33 (d, J = 5.4 Hz, 1H), 7.10 (dd, J = 4.9, 6.6 Hz, 1H), 7.22 (ddd, J = 1.2, 2.4, 9.3 Hz, 1H), 7.36 - 7.37 (m, 2H), 7.57 (ddd, J = 1.7, 7.8, 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 8.23 (d, J = 9.3 Hz, 1H), 8.48 - 8.49 (m, 2H)
Mass spectrometric value (ESI-MS, m/z): 410 $(M+Na)^+$

[0356] Example 144: 2-[4-(5,6-Dimethyl-[2,2′]bipyridinyl-3-yloxy)-7-methoxy-quinolin-6-yloxy]-ethanol (compound 144)

4-(5,6-Dimethyl-[2,2′]bipyridinyl-3-yloxy)-7-methoxy-quinolin-6-ol (compound 141) (88 mg) was dissolved in N,N-dimethylformamide (3 ml). Potassium carbonate (200 mg) and 2-bromoethanol (0.2 ml) were added to the solution, and the mixture was stirred at 70°C overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a methanol-chloroform system to give the title compound (59 mg, yield 67%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.38 (s, 3H), 2.65 (s, 3H), 4.00 (s, 3H), 4.04 (t, J = 4.4 Hz, 2H), 4.27 (t, J = 4.6 Hz, 2H), 6.37 (d, J = 5.4 Hz, 1H), 7.12 (dd, J = 4.9, 6.6 Hz, 1H), 7.33 (s, 1H), 7.37 (s, 1H), 7.58 (s, 1H), 7.59 (ddd, J = 2.0, 7.8, 7.8 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 8.40 (d, J = 5.4 Hz, 1H), 8.50 (m, 1H)
Mass spectrometric value (ESI-MS, m/z): 440 $(M+Na)^+$

[0357] Example 145: 4-(5,6-Dimethyl-[2,2′]bipyridinyl-3-yloxy)-6-methoxy-quinoline-7-carboxylic acid amide (compound 145)

Methyl 2-methoxy-5-nitro-benzoate (300 mg), ammonium chloride (228 mg), and zinc (929 mg) were suspended in ethanol (10 ml) and water (0.5 ml), and the suspension was stirred under reflux for 3 hr. The reaction mixture was filtered, and the solvent was removed from the filtrate by distillation under the reduced pressure. A saturated aqueous sodium hydrogencarbonate solution was added to the residue, and the mixture was extracted with chloroform, and the chloroform layer was washed with water and saturated brine and was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an acetone-chloroform system to give methyl 5-amino-2-methoxy-benzoate (244 mg, yield 95%).

Methyl 5-amino-2-methoxy-benzoate (244 mg) and 5-methoxymethylene-2,2-dimethyl-[1,3]dioxan-4,6-dione (228 mg) were dissolved in 2-propanol (3 ml), and the mixture was stirred at 100°C for 15 hr. The solvent was removed by distillation under the reduced pressure, and the residue was washed with diethyl ether to give methyl 5-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-2-methoxy-benzoate (248 mg, yield 55%).

[0358] Methyl 5-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-2-methoxy-benzoate (245 mg) and biphenyl (676 mg) were suspended in diphenyl ether (2 ml), and the suspension was stirred at 260°C for 45 min. The reaction mixture was cooled to room temperature, and the precipitated crystal was collected by filtration and was washed with diethyl ether. The crystal thus obtained as such was used in the next reaction without further purification.

The crystal (45 mg) was suspended in thionyl chloride (1 ml), a minor amount of dimethylformamide was added to the suspension, and the mixture was stirred at 100°C for 3.5 hr. The reaction mixture was added to a saturated aqueous sodium hydrogencarbonate solution under ice cooling.

The mixture was extracted with chloroform, and the chloroform layer was washed with water and saturated brine and was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an acetone-chloroform system to give methyl 4-chloro-6-methoxy-quinoline-7-carboxylate (4 mg, yield 2%) (2 steps).

Methyl 4-chloro-6-methoxy-quinoline-7-carboxylate (99 mg) was dissolved in methanol (5 ml). A 28% aqueous ammonia solution (5 ml) was added to the solution, and the mixture was stirred at 40°C overnight. Methanol was removed by distillation under the reduced pressure, and ethyl acetate was added to the residue for extraction. The ethyl acetate layer was washed with water and saturated brine and was dried over magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a methanol-chloroform system to give 4-chloro-6-methoxy-quinoline-carboxylic acid amide (85 mg, yield 91%).

[0359] 4-Chloro-6-methoxy-quinoline-carboxylic acid amide (41 mg), 5,6-dimethyl-[2,2′]bipyridinyl-3-ol (87 mg), 4-dimethylaminopyridine (63 mg), and cesium carbonate (169 mg) were suspended in dimethylsulfoxide (2 ml), and the suspension was stirred at 120°C for 22 hr. The reaction mixture was cooled to room temperature, and water was added thereto. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was then washed with water and saturated brine and was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a chloroform-methanol system to give the title compound (13 mg, yield 19%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.66 (s, 3H), 4.10 (s, 3H), 6.03 (brs, 1H), 6.46 (d, J = 5.2 Hz, 1H), 7.11 (m, 1H), 7.38 (s, 1H), 7.60 (m, 1H), 7.71 (m, 2H), 7.82 (d, J = 7.6 Hz,

1H), 8.44 (dd, J = 4.8, 0.8 Hz, 1H), 8.53 (d, J = 5.2 Hz, 1H), 8.89 (s, 1H)
Mass spectrometric value (ESI-MS, m/z): 423 $(M+Na)^+$

[0360] Example 146: 7-Chloro-4-(5,6-dimethyl-[2,2']bipyridinyl-3-yloxy)-quinoline-6-carboxylic acid amide (compound 146)

4-Amino-2-chloro-benzoic acid (2.50 g) and lithium hydroxide monohydrate (611 mg) were suspended in tetrahydrofuran (20 ml), and the suspension was stirred at room temperature for 20 min. Thereafter, dimethylsulfuric acid (1.38 ml) was added to the reaction mixture, and the mixture was stirred under reflux for 2 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was neutralized with a saturated aqueous sodium hydrogencarbonate solution and was extracted with diethyl ether. The diethyl ether layer was then washed with water and saturated brine and was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure to give methyl 4-amino-2-chloro-benzoate (1.68 g, yield 62%).

Methyl 4-amino-2-chloro-benzoate (1.68 g) and 5-methoxymethylene-2,2-dimethyl-[1,3]dioxan-4,6-dione (1.53 g) were dissolved in 2-propanol (25 ml), and the mixture was stirred at 100°C for 15.5 hr. The solvent was removed by distillation under the reduced pressure, and the residue was washed with diethyl ether to give methyl 2-chloro-4-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-benzoate (1.92 g, yield 63%).

[0361] Methyl 2-chloro-4-[(2,2-dimethyl-4,6-dioxo-[1,3]dioxan-5-ylidenemethyl)-amino]-benzoate (1.81 g) and biphenyl (4.93 g) were suspended in diphenyl ether (12 ml), and the suspension was stirred at 260°C for 45 min. The reaction mixture was cooled to room temperature, and the precipitated crystal was collected by filtration and was washed with diethyl ether. The crystal

thus obtained as such was used in the next reaction without further purification.

The crystal (1.21 g) was suspended in thionyl chloride (12 ml), a minor amount of N,N-dimethylformamide was added to the suspension, and the mixture was stirred at 100°C for 4 hr. The reaction mixture was added to a saturated aqueous sodium hydrogencarbonate solution under ice cooling. The mixture was extracted with chloroform, and the chloroform layer was washed with water and saturated brine and was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an acetone-hexane system to give methyl 4,7-dichloro-quinoline-6-carboxylate (350 mg, yield 26%) (2 steps).

Methyl 4,7-dichloro-quinoline-6-carboxylate (197 mg) was dissolved in methanol (7 ml). A 28% aqueous ammonia solution (7 ml) was added to the solution, and the mixture was stirred at 40°C overnight. Methanol was removed by distillation under the reduced pressure, and ethyl acetate was added to the residue for extraction. The ethyl acetate layer was washed with water and saturated brine and was dried over magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a methanol-chloroform system to give 4,7-dichloro-quinoline-6-carboxylic acid amide (145 mg, yield 78%).

[0362] 4,7-Dichloro-quinoline-6-carboxylic acid amide (50 mg), 5,6-dimethyl-[2,2′]bipyridinyl-3-ol (83 mg), 4-dimethylaminopyridine (76 mg), and cesium carbonate (203 mg) were suspended in dimethylsulfoxide (2 ml), and the suspension was stirred at 120°C for 22 hr. The reaction mixture was cooled to room temperature, and water was added thereto. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was then washed with water and saturated brine and was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure,

and the residue was purified by thin layer chromatography with a chloroform-methanol system to give the title compound (16 mg, yield 19%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.65 (s, 3H), 6.36 (brs, 1H), 6.44 (d, J = 5.2 Hz, 1H), 6.62 (brs, 1H), 7.08 (ddd, J = 7.2, 4.8, 1.2 Hz, 1H), 7.35 (s, 1H), 7.60 (m, 1H), 7.86 (m, 1H), 8.09 (s, 1H), 8.36 (m, 1H), 8.59 (d, J = 5.2 Hz, 1H), 8.76 (s, 1H)

Mass spectrometric value (ESI-MS, m/z): 427 $(M+Na)^+$

[0363] Example 147: 6-Methoxy-4-(2-phenyl-[1,8]naphthyridin-3-yloxy)-quinoline-7-carboxylic acid amide (compound 147)

4-Chloro-6-methoxy-quinoline-7-carboxylic acid amide (21 mg), 2-phenyl-[1,8]naphthyridin-3-ol (49 mg), and 4-dimethylaminopyridine (33 mg) were suspended in 1,2-dichlorobenzene (1.5 ml), and the suspension was stirred at 140°C for 3.5 hr. The reaction mixture was cooled to room temperature, and water was added thereto. The mixture was extracted with chloroform, and the chloroform layer was washed with water and saturated brine and was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a chloroform-methanol system to give the title compound (26 mg, yield 69%).

^{1}H-NMR (CD_3OD, 400 MHz): δ 4.11 (s, 3H), 6.66 (d, J = 5.6 Hz, 1H), 7.32 (m, 3H), 7.70 (dd, J = 8.4, 4.4 Hz, 1H), 7.89 (s, 1H), 8.01 (m, 2H), 8.39 - 8.52 (m, 4H), 9.11 (d, J = 2.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 445 $(M+Na)^+$

[0364] Example 148: Methyl 7-chloro-4-(2-phenyl-[1,8]naphthyridin-3-yloxy)-quinoline-6-carboxylate (compound 148)

Methyl 4,7-dichloro-quinoline-6-carboxylate (46 mg), 2-phenyl-[1,8]naphthyridin-3-ol (100 mg), and 4-dimethylaminopyridine (66 mg) were suspended in

1,2-dichlorobenzene (1.5 ml), and the suspension was stirred at 140°C for 3.5 hr. The reaction mixture was cooled to room temperature, and water was added thereto. The mixture was extracted with chloroform, and the chloroform layer was washed with water and saturated brine and was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a chloroform-methanol system to give the title compound (33 mg, yield 42%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.03 (s, 3H), 6.44 (d, J = 5.2 Hz, 1H), 7.33 (m, 3H), 7.56 (dd, J = 8.0, 4.4 Hz, 1H), 8.07 (m, 3H), 8.15 (s, 1H), 8.21 (dd, J = 8.4, 2.0 Hz, 1H), 8.63 (d, J = 5.2 Hz, 1H), 8.89 (s, 1H), 9.19 (dd, J = 4.4, 2.0 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 464 $(M+Na)^+$

[0365] <u>Example 154: 2-[4-(5,6-Dimethyl-[2,2′]bipyridinyl-3-yloxy)-7-methoxy-quinolin-6-ylamino]-ethanol (compound 154)</u>

Palladium acetate (30 mg) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (80 mg) were dissolved in toluene (4 ml), and the solution was stirred at room temperature for 5 min. 3-(6-Bromo-7-methoxy-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 133) (100 mg) and 2-aminoethanol (0.2 ml) were added thereto, and the mixture was stirred at room temperature for additional 5 min. Cesium carbonate (250 mg) was added to the reaction mixture, and the mixture was stirred at 80°C for two days. Water was added to the reaction mixture, the mixture was extracted with chloroform, and the chloroform layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (9 mg, yield 9%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.27 (s, 3H), 2.56 (s, 3H), 3.35 (t,

J = 5.4 Hz, 2H), 3.82 (t, J = 5.4 Hz, 2H), 3.88 (s, 3H), 6.32 (d, J = 5.1 Hz, 1H), 7.00 (m, 1H), 7.07 (ddd, J = 1.0, 4.9, 7.6 Hz, 1H), 7.19 - 7.20 (m, 2H), 7.52 (ddd, J = 1.7, 7.8, 8.1 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 8.21 (d, J = 5.1 Hz, 1H), 8.51 (m, 1H)
Mass spectrometric value (ESI-MS, m/z): 439 $(M+Na)^+$

[0366] Example 155: 3-(7-Methoxy-6-pyridin-3-yl-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 155)

N,N-Dimethylformamide (3 ml) and a 2 M aqueous potassium carbonate solution (1.5 ml) were added to 3-(6-bromo-7-methoxy-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 133) (70 mg), tetrakistriphenylphosphine palladium (29 mg), and 3-pyridylboric acid (57 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 2 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-methanol system to give the title compound (56 mg, yield 80%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.66 (s, 3H), 3.98 (s, 3H), 6.35 (d, J = 5.4 Hz, 1H), 7.10 (dd, J = 5.8, 7.6 Hz, 1H), 7.36 - 7.39 (m, 2H), 7.48 (s, 1H), 7.59 (ddd, J = 1.7, 7.6, 7.8 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 8.25 (s, 1H), 8.47 (m, 1H), 8.51 (d, J = 5.4 Hz, 1H), 8.61 (m, 1H), 8.85 (m, 1H)
Mass spectrometric value (ESI-MS, m/z): 457 $(M+Na)^+$

[0367] Example 156: 3-(6-Chloro-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 156)

4,6-Dichloro-quinoline (50 mg), 5,6-dimethyl-[2,2']bipyridinyl-3-ol (51 mg), and

4-dimethylaminopyridine (93 mg) were dissolved in dimethylsulfoxide (1.5 ml), cesium carbonate (247 mg) was added to the solution, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The organic layer was extracted with chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (90 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.67 (s, 3H), 6.51 (d, J = 5.4 Hz, 1H), 7.11 (ddd, J = 1.0, 4.9, 7.6 Hz, 1H), 7.38 (s, 1H), 7.63 (ddd, J = 1.7, 7.8, 7.8 Hz, 1H), 7.73 (dd, J = 2.2, 8.8 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.34 (m, 1H), 8.37 (d, J = 2.2 Hz, 1H), 8.56 (d, J = 5.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 384 $(M+Na)^+$

[0368] <u>Example 157: 5,6-Dimethyl-3-(6-methyl-quinolin-4-yloxy)-[2,2']bipyridine (compound 157)</u>

4-Chloro-6-methyl-quinoline (50 mg), 5,6-dimethyl-[2,2']bipyridinyl-3-ol (56 mg), and 4-dimethylaminopyridine (103 mg) were dissolved in dimethylsulfoxide (1.5 ml), cesium carbonate (275 mg) was added to the solution, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The organic layer was extracted with chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (82 mg, yield 85%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.58 (s, 3H), 2.67 (s, 3H), 6.46 (d, J = 5.4 Hz, 1H), 7.10 (ddd, J = 1.2, 4.9, 7.6 Hz, 1H), 7.36 (s, 1H), 7.60 (m, 1H), 7.64 (s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 8.15 (m, 1H), 8.40 (m, 1H), 8.51 (d, J = 5.4 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 364 $(M+Na)^+$

[0369] Example 158: 4-(5,6-Dimethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-6-fluoro-7-methoxy-quinoline (compound 158)

4-Chloro-6-fluoro-7-methoxy-quinoline (13 mg), 5,6-dimethyl-2-pyrimidin-2-yl-pyridin-3-ol (12 mg), and 4-dimethylaminopyridine (22 mg) were dissolved in dimethylsulfoxide (1 ml), cesium carbonate (58 mg) was added to the solution, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The organic layer was extracted with chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (15 mg, yield 66%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.44 (s, 3H), 2.70 (s, 3H), 4.07 (s, 3H), 6.48 (d, J = 5.4 Hz, 1H), 7.12 (t, J = 4.9 Hz, 1H), 7.43 (s, 1H), 7.65 (m, 1H), 7.95 (d, J = 11.5 Hz, 1H), 8.48 (d, J = 5.6 Hz, 1H), 8.62 (d, J = 4.9 Hz, 2H)
Mass spectrometric value (ESI-MS, m/z): 399 $(M+Na)^+$

[0370] Example 159: 4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-6-fluoro-7-methoxy-quinoline (compound 159)

4-Chloro-6-fluoro-7-methoxy-quinoline (50 mg), 6-ethyl-2-pyrimidin-2-yl-pyridin-3-ol(48 mg), and 4-dimethylaminopyridine (84 mg) were dissolved in dimethylsulfoxide (1.5 ml), cesium carbonate (231 mg) was

added to the solution, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The organic layer was extracted with chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (54 mg, yield 60%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.42 (t, J = 7.8 Hz, 3H), 3.06 (q, J = 7.6 Hz, 2H), 4.06 (s, 3H), 6.51 (d, J = 5.4 Hz, 1H), 7.14 (t, J = 4.9 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.61 (m, 2H), 7.92 (d, J = 10.7 Hz, 1H), 8.50 (d, J = 5.4 Hz, 1H), 8.65 (d, J = 4.9 Hz, 2H)

Mass spectrometric value (ESI-MS, m/z): 399 $(M+Na)^+$

[0371] Example 160: 3-(6-Fluoro-7-methoxy-quinolin-4-yloxy)-2-methyl-[1,8]naphthyridine (compound 160)

2-Methyl-[1,8]naphthyridin-3-ol (42 mg), 4-chloro-6-fluoro-7-methoxy-quinoline (50 mg), and 4-dimethylaminopyridine (87 mg) were suspended in 1,2-dichlorobenzene (1.5 ml), and the suspension was stirred at 130°C for 5 hr. The reaction mixture was cooled to room temperature, and an aqueous sodium hydrogencarbonate solution was added to the reaction mixture. The organic layer was extracted with chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (63 mg, yield 78%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.73 (s, 3H), 4.11 (s, 3H), 6.49 (d, J = 5.4 Hz, 1H), 7.52 (dd, J = 4.4, 8.3 Hz, 1H), 7.74 (d, J = 7.8

Hz, 1H), 7.84 (s, 1H), 8.01 (d, J = 11.2 Hz, 1H), 8.15 (dd, J = 2.0, 8.1 Hz, 1H), 8.63 (d, J = 5.4 Hz, 1H), 9.14 (dd, J = 2.0, 4.4 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 358 $(M+Na)^+$

[0372] Example 161: 2-Ethyl-3-(6-fluoro-7-methoxy-quinolin-4-yloxy)-[1,8]naphthyridine (compound 161)

2-Aminopyridine-3-carbaldehyde (100 mg) and 1-bromo-butan-2-one (124 mg) were suspended in a 5 N aqueous sodium hydroxide solution (0.6 ml), and the suspension was allowed to stand in a hermetically stoppered state for three days. The reaction mixture was neutralized with 10% hydrochloric acid, and the resultant precipitate was filtered, and the residue was washed with water and chloroform. The powder was dried in vacuo to give 2-ethyl-[1,8]naphthyridin-3-ol (106 mg, yield 74%).

2-Ethyl-[1,8]naphthyridin-3-ol (41 mg), 4-chloro-6-fluoro-7-methoxy-quinoline (50 mg), and 4-dimethylaminopyridine (87 mg) were suspended in 1,2-dichlorobenzene (1.5 ml), and the suspension was stirred at 130°C for 6.5 hr. The reaction mixture was cooled to room temperature, and an aqueous sodium hydrogencarbonate solution was added to the reaction mixture. The organic layer was extracted with chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (38 mg, yield 46%).。

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.45 (t, J = 7.6 Hz, 3H), 3.04 (q, J = 7.3 Hz, 2H), 4.10 (s, 3H), 6.50 (d, J = 5.4 Hz, 1H), 7.51 (dd, J = 4.4, 7.6 Hz, 1H), 7.69 (m, 1H), 7.82 (s, 1H), 7.99 (dd, J = 1.2, 11.2 Hz, 1H), 8.14 (dd, J = 1.5, 8.3 Hz, 1H), 8.63 (d, J = 5.4 Hz, 1H), 9.14 (ddd, J = 1.0, 2.0, 4.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 372 $(M+Na)^+$

[0373] Example 162: 6-Ethyl-3-(6-fluoro-7-methoxy-quinolin-4-yloxy)-[2,2′]bipyridine (compound 162)

4-Chloro-6-fluoro-7-methoxy-quinoline (50 mg), 6-ethyl-[2,2′]bipyridinyl-3-ol (52 mg), and 4-dimethylaminopyridine (87 mg) were dissolved in dimethylsulfoxide (1.5 ml), cesium carbonate (231 mg) was added to the solution, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The organic layer was extracted with chloroform, and the chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (84 mg, yield 93%).

^1H-NMR ($CDCl_3$, 400 MHz): δ 1.42 (t, J = 7.8 Hz, 3H), 3.01 (q, J = 7.6 Hz, 2H), 4.06 (s, 3H), 6.43 (d, J = 5.6 Hz, 1H), 7.12 (ddd, J = 1.2, 4.9, 7.6 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.63 - 7.67 (m, 2H), 7.92 (d, J = 7.8 Hz, 1H), 7.96 (d, J = 11.5 Hz, 1H), 8.33 (d, J = 3.9 Hz, 1H), 8.47 (d, J = 5.6 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 398 $(M+Na)^+$

[0374] Example 163: 5,6-Dimethyl-3-(6-thiophen-3-yl-quinolin-4-yloxy)-[2,2′]bipyridine (compound 163)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 2) (30 mg), tetrakistriphenylphosphine palladium (9 mg), and thiophene-3-boric acid (28 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 5 hr. The

reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-acetone system to give the title compound (30 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 2.67 (s, 3H), 6.45 (d, J = 5.1 Hz, 1H), 7.09 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.39 (s, 1H), 7.44 (dd, J = 5.1, 2.9 Hz, 1H), 7.54 - 7.60 (m, 2H), 7.64 (dd, J = 2.9, 1.5 Hz, 1H), 7.83 (ddd, J = 7.1, 1.0, 1.0 Hz, 1H), 8.00 (dd, J = 8.8, 2.0 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 8.47 - 8.51 (m, 1H), 8.52 - 8.56 (m, 2H)

Mass spectrometric value (ESI-MS, m/z): 410 $(M+1)^+$

[0375] Example 164: 3-(6-Benzo[b]thiophen-3-yl-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 164)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 2) (30 mg), tetrakistriphenylphosphine palladium (9 mg), and thianaphthene-3-boric acid (39 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water

and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-acetone system to give the title compound (34 mg, yield 100%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.66 (s, 3H), 6.50 (d, J = 5.1 Hz, 1H), 7.11 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.36 - 7.44 (m, 3H), 7.54 - 7.62 (m, 2H), 7.83 (ddd, J = 8.0, 1.0, 1.0 Hz, 1H), 7.92 - 8.01 (m, 3H), 8.16 (d, J = 8.6 Hz, 1H), 8.48 - 8.53 (m, 1H), 8.55 (d, J = 2.0 Hz, 1H), 8.61 (d, J = 5.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 482 $(M+Na)^+$

[0376] <u>Example 165: 5,6-Dimethyl-3-[6-(5-methyl-thiophen-2-yl)-quinolin-4-yloxy]-[2,2']bipyridine (compound 165)</u>

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 2) (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 5-methylthiophene-2-boric acid (31 mg) under an argon atmosphere, and the mixture was stirred at 70°C overnight. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a hexane-acetone system to give the title compound (4 mg, yield 13%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.55 (s, 3H), 2.67 (s, 3H), 6.43 (d, J = 4.9 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 7.06 - 7.14 (m, 1H), 7.29 (d, J = 3.2 Hz, 1H), 7.39 (s, 1H), 7.54 -

7.62 (m, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.95 (dd, J = 8.8, 2.0 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 8.45 (s, 1H), 8.47 - 8.55 (m, 2H)

Mass spectrometric value (ESI-MS, m/z): 424 $(M+1)^+$

Example 166: 3-(6-Benzofuran-2-yl-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 166)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 2) (30 mg), tetrakistriphenylphosphine palladium (9 mg), and benzo[b]furan-2-boric acid (36 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-acetone system to give the title compound (4 mg, yield 13%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.68 (s, 3H), 6.46 (d, J = 5.1 Hz, 1H), 7.08 (ddd, J = 8.8, 4.9, 1.2 Hz, 1H), 7.20 (d, J = 0.8 Hz, 1H), 7.23 - 7.34 (m, 2H), 7.41 (s, 1H), 7.51 - 7.65 (m, 3H), 7.89 (ddd, J = 7.8, 7.8, 1.0 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.17 (dd, J = 8.8, 2.0 Hz, 1H), 8.47 - 8.51 (m, 1H), 8.55 (d, J = 5.1 Hz, 1H), 8.87 (d, J = 1.8 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 466 $(M+Na)^+$

[0377] Example 167: 2-[4-(5,6-Dimethyl-[2,2']bipyridinyl-3-yloxy)-quinolin-6-yl]-pyrr

ole-1-carboxylate tert-butyl ester (compound 167)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 2) (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 1-(tert-butoxycarbonyl)pyrrole-2-boric acid (47 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-acetone system to give the title compound (31 mg, yield 85%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.37 (s, 9H), 2.38 (s, 3H), 2.66 (s, 3H), 6.27 (dd, J = 3.2, 3.2 Hz, 1H), 6.31 - 6.35 (m, 1H), 6.45 (d, J = 5.1 Hz, 1H), 7.10 (dd, J = 7.1, 5.1 Hz, 1H), 7.34 (s, 1H), 7.38 - 7.43 (m, 1H), 7.57 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.73 (dd, J = 8.8, 1.7 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 8.31 (d, J = 1.7 Hz, 1H), 8.52 (d, J = 4.4 Hz, 1H), 8.56 (d, J = 5.2 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 515 $(M+Na)^+$

[0378] Example 168: 5,6-Dimethyl-3-[6-(1H-pyrrol-2-yl)-quinolin-4-yloxy]-[2,2′]bipyridine (compound 168)

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 2) (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 1-(tert-butoxycarbonyl)pyrrole-2-boric acid (47 mg)

under an argon atmosphere, and the mixture was stirred at 70°C for 5 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-acetone system to give the title compound (4 mg, yield 15%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H), 2.63 (s, 3H), 6.32 - 6.37 (m, 1H), 6.47 (d, J = 5.1 Hz, 1H), 6.70 - 6.74 (m, 1H), 6.94 - 6.98 (m, 1H), 7.08 - 7.15 (m, 1H), 7.29 (s, 1H), 7.60 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.95 (dd, J = 9.0, 2.2 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 8.36 (d, J = 1.7 Hz, 1H), 8.47 - 8.52 (m, 2H)

Mass spectrometric value (ESI-MS, m/z): 393 $(M+1)^+$

[0379] <u>Example 169: 5,6-Dimethyl-3-[6-(1H-pyrazol-4-yl)-quinolin-4-yloxy]-[2,2′]bipyridine (compound 169)</u>

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2′]bipyridine (compound 2) (30 mg), tetrakistriphenylphosphine palladium (9 mg), and 1H-pyrazole-4-boric acid pinacol ester (43 mg) under an argon atmosphere, and the mixture was stirred at 70°C overnight. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium

carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-acetone system to give the title compound (10 mg, yield 33%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.67 (s, 3H), 6.45 (d, J = 5.1 Hz, 1H), 7.07 - 7.13 (m, 1H), 7.39 (s, 1H), 7.59 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.91 (dd, J = 8.8, 2.2 Hz, 1H), 8.03 (s, 2H), 8.06 (d, J = 8.8 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 8.48 - 8.51 (m, 1H), 8.53 (d, J = 5.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 394 $(M+1)^+$

[0380] Example 170: 3-(6,7-Dimethyl-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 170)

3,4-Dimethylaniline (3.0 g) was dissolved in 2-propanol (70 ml), and the mixture was stirred at 70°C for 10 min. 5-(Methoxymethylene)-2,2-dimethyl-[1,3]dioxan-4,6-dione (5.1 g) was added thereto, and the mixture was stirred at 70°C for one hr. The reaction mixture was cooled to room temperature, and the solvent was removed by distillation under the reduced pressure. The residue was suspended in diethyl ether, was collected by filtration, and was washed with diethyl ether. The crude crystal thus obtained as such was used in the next reaction without purification.

Diphenyl ether (50 ml) was added to the crude crystal obtained above and biphenyl (22.2 g), and the mixture was stirred at 240°C for 3 hr. The reaction mixture was cooled to room temperature. Diethyl ether and hexane were added to the cooled reaction mixture, and the resultant precipitate was collected by filtration and was washed with diethyl ether. The crude crystal thus obtained as such was used in the next reaction without purification.

[0381] Thionyl chloride (10 ml) and a minor amount of

N,N-dimethylformamide were added to the crude crystal, and the mixture was stirred under reflux for 3 hr. The reaction mixture was added to a saturated aqueous sodium bicarbonate solution under ice cooling, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-ethyl acetate system to give 4-chloro-6,7-dimethylquinoline (1.07 g, yield 31%).

Dimethylsulfoxide (2 ml) was added to 5,6-dimethyl-[2,2']bipyridinyl-3-ol (40 mg), 4-chloro-6,7-dimethylquinoline (115 mg), cesium carbonate(196 mg), and 4-dimethylaminopyridine (73 mg), and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-acetone system to give the title compound (27 mg, yield 38%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.36 (s, 3H), 2.48 (s, 3H), 2.65 (s, 3H), 2.79 (s, 3H), 6.48 (d, J = 4.9 Hz, 1H), 7.14 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.26 (s, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.61 (ddd, J = 7.6, 7.6, 1.9 Hz, 1H), 7.76 - 7.83 (m, 2H), 8.48 (d, J = 5.1 Hz, 1H), 8.53 - 8.58 (m, 1H)

Mass spectrometric value (ESI-MS, m/z): 378 $(M+Na)^+$

[0382] <u>Example 171: 5,6-Dimethyl-3-(7-thiophen-3-yl-quinolin-4-yloxy)-[2,2']bipyridine (compound 171)</u>

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(7-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 14) (30 mg), tetrakistriphenylphosphine palladium

(9 mg), and thiophene-3-boric acid (28 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 7 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-acetone system to give the title compound (18 mg, yield 59%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.67 (s, 3H), 6.41 (d, J = 5.4 Hz, 1H), 7.10 (ddd, J = 7.6, 4.6, 1.0 Hz, 1H), 7.39 (s, 1H), 7.46 (dd, J = 4.9, 3.0 Hz, 1H), 7.55 - 7.61 (m, 2H), 7.68 (dd, J = 2.9, 1.2 Hz, 1H), 7.81 - 7.86 (m, 2H), 8.26 (d, J = 1.7 Hz, 1H), 8.36 (d, J = 8.6 Hz, 1H), 8.48 - 8.52 (m, 1H), 8.57 (d, J = 5.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 410 $(M+1)^+$

[0383] <u>Example 172: 3-(7-Benzo[b]thiophen-3-yl-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 172)</u>

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(7-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 14) (30 mg), tetrakistriphenylphosphine palladium (9 mg), and thianaphthene-3-boric acid (39 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 7 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by

the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-acetone system to give the title compound (33 mg, yield 96%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.68 (s, 3H), 6.47 (d, J = 5.1 Hz, 1H), 7.12 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.39 - 7.46 (m, 3H), 7.58 - 7.64 (m, 2H), 7.82 (dd, J = 8.6, 1.7 Hz, 1H), 7.87 (ddd, J = 7.8, 1.0, 1.0 Hz, 1H), 7.92 - 7.97 (m, 1H), 8.02 - 8.09 (m, 1H), 8.30 (d, J = 1.7 Hz, 1H), 8.45 (d, J = 8.8 Hz, 1H), 8.51 - 8.55 (m, 1H), 8.62 (d, J = 5.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 460 $(M+1)^+$

[0384] <u>Example 173: 3-(7-Benzofuran-2-yl-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 173)</u>

N,N-Dimethylformamide (1 ml) and a 2 M aqueous potassium carbonate solution (0.5 ml) were added to 3-(7-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 14) (30 mg), tetrakistriphenylphosphine palladium (9 mg), and benzo[b]furan-2-boric acid (36 mg) under an argon atmosphere, and the mixture was stirred at 70°C for 7 hr. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-acetone system to give the title compound (26 mg, yield 78%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.67 (s, 3H), 6.43 (d, J = 5.1 Hz, 1H), 7.09 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.23 - 7.29 (m, 2H), 7.33 (ddd, J = 8.3, 8.3, 1.4 Hz, 1H), 7.40 (s, 1H), 7.55 - 7.61 (m, 2H), 7.64 (d, J = 7.6 Hz, 1H), 7.84 (ddd, J = 7.8, 1.2, 1.2 Hz, 1H), 8.03 (dd, J = 8.8, 1.7 Hz, 1H), 8.41 (d, J = 8.8 Hz, 1H), 8.46 - 8.51 (m, 1H), 8.54 (d, J = 1.4 Hz, 1H), 8.59 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 444 $(M+1)^+$

[0385] Example 174: 5,6-Dimethyl-3-(6-pyridin-2-yl-quinolin-4-yloxy)-[2,2']bipyridine (compound 174)

N,N-Dimethylformamide (1 ml) was added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 2) (25 mg), tetrakistriphenylphosphine palladium (7 mg), 2-tributylstannylpyridine (45 mg), and copper(II) oxide (1 mg) under an argon atmosphere, and the mixture was stirred at 100°C overnight. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a hexane-acetone system to give the title compound (12 mg, yield 46%).
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.67 (s, 3H), 6.46 (d, J = 5.1 Hz, 1H), 7.08 (ddd, J = 7.3, 4.6, 1.0 Hz, 1H), 7.27 - 7.32 (m, 1H), 7.39 (s, 1H), 7.56 (ddd, J = 7.8, 7.8, 1.9 Hz, 1H), 7.81 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.44 (dd, J = 8.8, 2.0 Hz, 1H), 8.47 - 8.51 (m, 1H), 8.58 (d, J = 5.1 Hz, 1H), 8.74 - 8.79 (m, 1H), 8.96 (d, J = 2.0 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 405 $(M+1)^+$

[0386] Example 175: 5,6-Dimethyl-3-(6-pyrimidin-2-yl-quinolin-4-yloxy)-[2,2']bipyridine (compound 175)

N,N-Dimethylformamide (1 ml) was added to 3-(6-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 2) (25 mg), tetrakistriphenylphosphine palladium (7 mg), 2-tributylstannylpyrimidine (45 mg), and copper(II) oxide (1 mg) under an argon atmosphere, and the mixture was stirred at 100°C overnight. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a hexane-acetone system to give the title compound (6 mg, yield 22%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.68 (s, 3H), 6.46 (d, J = 5.2 Hz, 1H), 7.07 (ddd, J = 7.6, 4.9, 1.0 Hz, 1H), 7.24 - 7.28 (m, 1H), 7.39 (s, 1H), 7.53 (ddd, J = 7.8, 7.8, 2.0 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.48 - 8.53 (m, 1H), 8.60 (d, J = 5.1 Hz, 1H), 8.81 (dd, J = 8.8, 2.0 Hz, 1H), 8.88 (d, J = 4.9 Hz, 2H), 9.48 (d, J = 1.7 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 428 $(M+Na)^+$

[0387] Example 176: 5,6-Dimethyl-3-(7-pyridin-2-yl-quinolin-4-yloxy)-[2,2']bipyridine (compound 176)

N,N-Dimethylformamide (1 ml) was added to 3-(7-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 14) (25 mg), tetrakistriphenylphosphine palladium

(7 mg), 2-tributylstannylpyridine (45 mg), and copper(II) oxide (1 mg) under an argon atmosphere, and the mixture was stirred at 100°C overnight. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a hexane-acetone system to give the title compound (18 mg, yield 72%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.67 (s, 3H), 6.45 (d, J = 5.1 Hz, 1H), 7.08 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.28 - 7.34 (m, 1H), 7.42 (s, 1H), 7.56 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.80 - 7.87 (m, 2H), 7.94 (d, J = 8.0 Hz, 1H), 8.35 (dd, J = 8.8, 1.7 Hz, 1H), 8.46 (d, J = 8.8 Hz, 1H), 8.47 - 8.51 (m, 1H), 8.58 (d, J = 1.5 Hz, 1H), 8.60 (d, J = 5.1 Hz, 1H), 8.75 - 8.80 (m, 1H)

Mass spectrometric value (ESI-MS, m/z): 427 $(M+Na)^+$

[0388] Example 177: 5,6-Dimethyl-3-(7-pyrimidin-2-yl-quinolin-4-yloxy)-[2,2']bipyridine (compound 177)

N,N-Dimethylformamide (1 ml) was added to 3-(7-bromo-quinolin-4-yloxy)-5,6-dimethyl-[2,2']bipyridine (compound 14) (25 mg), tetrakistriphenylphosphine palladium (7 mg), 2-tributylstannylpyrimidine (45 mg), and copper(II) oxide (1 mg) under an argon atmosphere, and the mixture was stirred at 100°C overnight. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid, and the aqueous layer was washed with ethyl acetate. The aqueous

layer was rendered alkaline by the addition of potassium carbonate and was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was then dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a hexane-acetone system to give the title compound (6 mg, yield 24%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.67 (s, 3H), 6.46 (d, J = 5.2 Hz, 1H), 7.08 (ddd, J = 7.6, 4.9, 1.2 Hz, 1H), 7.25 - 7.29 (m, 1H), 7.42 (s, 1H), 7.56 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 8.44 - 8.51 (m, 2H), 8.61 (d, J = 2.7 Hz, 1H), 8.63 (d, J = 2.4 Hz, 1H), 8.90 (d, J = 4.9 Hz, 2H), 9.16 (d, J = 1.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 428 $(M+Na)^+$

[0389] Examples 178 to 225

Compounds of Examples 178 to 225 were produced according to the above schemes. The names of compounds produced in these Examples and the measured values of the molecular weight of the actually produced compounds were as shown in Table A which will be described later.

For typical examples thereof, specific production processes will be described.

[0390] Example 178: 2-[6-Methoxy-4-(2-phenyl-[1,8]naphthyridin-3-yloxy)-quinolin-7-yloxy]-ethanol (compound 178)

2-Phenyl-[1,8]naphthyridin-3-ol (6.61 g), 7-benzyloxy-4-chloro-6-methoxy-quinoline (16.6 g), and 4-dimethylaminopyridine (10.9 g) were suspended in 1,2-dichlorobenzene (80 ml), and the suspension was stirred at 140°C for 20 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the

residue was purified by column chromatography with a methanol-chloroform system to give 3-(7-benzyloxy-6-methoxy-quinolin-4-yloxy)-2-phenyl-[1,8]naphthyridine (6.00 g, yield 42%).

3-(7-Benzyloxy-6-methoxy-quinolin-4-yloxy)-2-phenyl-[1,8]naphthyridine (4.36 g) was dissolved in trifluoroacetic acid (40 ml), methanesulfonic acid (3 ml) was added to the solution, and the mixture was stirred at 80°C for one hr. Water was added to the reaction mixture, the mixture was neutralized with an aqueous sodium hydrogencarbonate solution, and the organic layer was extracted with chloroform. The chloroform layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure to give 6-methoxy-4-(2-phenyl-[1,8]naphthyridin-3-yloxy)-quinolin-7-ol (3.55 g, yield 100%).

[0391]

6-Methoxy-4-(2-phenyl-[1,8]naphthyridin-3-yloxy)-quinolin-7-ol (3.55 g) was dissolved in N,N-dimethylformamide (30 ml). Potassium carbonate (6.20 g) and 2-bromoethanol (5.61 g) were added to the solution, and the mixture was stirred at 60°C overnight. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a methanol-chloroform system to give the title compound (3.20 g, yield 81%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.33 (m, 1H), 3.98 (s, 3H), 4.10 (m, 2H), 4.30(t, J = 4.8 Hz, 2H), 6.52 (d, J = 5.2 Hz, 1H), 7.37 (m, 3H), 7.44 (s, 1H), 7.48 (s, 1H), 7.92 (dd, J = 8.0, 4.0 Hz, 1H), 7.93 (s, 1H), 8.16 (m, 3H), 8.49 (d, J = 5.2 Hz, 1H), 9.16 (dd, J = 4.0, 2.0 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 462 $(M+Na)^+$

[0392] Example 181: 2-[4-(6-Ethyl-[2,2']bipyridinyl-3-yloxy)-quinolin-6-yloxy]-ethanol (compound 181)

2-Bromopyridine (500 mg) was dissolved in tetrahydrofuran (15 ml). A 1.58 M n-butyllithium/hexan solution (2 ml) was added to the solution, and the mixture was stirred at -78°C for 30 min. 5-Ethylfurfural (350 mg) was added to the reaction mixture, and the mixture was stirred at room temperature for additional one hr. Water was added to the reaction mixture, and the organic layer was extracted with ethyl acetate. The ethyl acetate layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with an ethyl acetate-hexane system to give (5-ethyl-furan-2-yl)-pyridin-2-yl-methanol (214 mg, yield 37%).

(5-Ethyl-furan-2-yl)-pyridin-2-yl-methanol (214 mg) was dissolved in chloroform (5 ml), manganese dioxide (1.37 g) was added to the solution, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered, and the solvent was removed by distillation under the reduced pressure. The residue was purified by thin layer chromatography with an ethyl acetate-hexane system to give (5-ethyl-furan-2-yl)-pyridin-2-yl-methanone (161 mg, yield 76%).

[0393] (5-Ethyl-furan-2-yl)-pyridin-2-yl-methanone (160 mg) was dissolved in methanol (3 ml), 28% aqueous ammonia (3 ml) was added to the solution, and the mixture was stirred in a sealed tube at 160°C overnight. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with an acetone-hexane system to give 6-ethyl-[2,2']bipyridin-3-ol (104 mg, yield 65%).

6-Benzyloxy-4-chloro-quinoline (3.47 g) and 6-ethyl-[2,2']bipyridin-3-ol (5.03 g) were dissolved in dimethylsulfoxide (25 ml), cesium carbonate (16.0 g) was

added to the solution, and the mixture was stirred at 140°C overnight. The reaction mixture was cooled to room temperature. Water was added to the reaction mixture, and the organic layer was extracted with ethyl acetate. The ethyl acetate layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue as such was used in the next reaction without purification.

The crude product prepared above was dissolved in trifluoroacetic acid (10 ml). Methanesulfonic acid (2 ml) was added to the solution, and the mixture was stirred at room temperature for 2 hr and then at 80°C for 7 hr. The reaction mixture was concentrated under the reduced pressure. Water was added to the reaction mixture, and the mixture was neutralized with an aqueous sodium hydrogencarbonate solution. The purified insolubles were collected by filtration and were washed with ethyl acetate to give 4-(6-ethyl-[2,2']bipyridinyl-3-yloxy)-quinolin-6-ol (2.57 g, yield 58%).

[0394] 4-(6-Ethyl-[2,2']bipyridinyl-3-yloxy)-quinolin-6-ol (2.57 g) was dissolved in N,N-dimethylformamide (25 ml). Potassium carbonate (9.08 g) and 2-bromoethanol (7.0 ml) were added to the solution, and the mixture was stirred at 80°C overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was washed with diethyl ether to give the title compound (1.29 g, yield 44%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.41(t, J = 7.8 Hz, 3H), 2.17 (m, 1H), 3.01(q, J = 7.8 Hz, 2H), 4.04 (m, 2H), 4.24 (t, J = 4.9 Hz, 2H), 6.45 (d, J = 5.1 Hz, 1H), 7.13 (ddd, J = 1.2, 4.9, 7.6 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.40 (dd, J = 2.9, 9.3 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 2.9 Hz, 1H), 7.62 (ddd, J

= 1.9, 7.8, 7.8 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 8.45 - 8.48 (m, 2H)
Mass spectrometric value (ESI-MS, m/z): 410 $(M+Na)^+$

[0395] Example 188: 4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-6,7-dimethoxy-quinoline (compound 188)

2-Methylfuran (4.92 g) was dissolved in anhydrous ether (80 ml). A 1.58 M n-butyllithium/hexan solution (31.6 ml) was added to the solution at 0°C, and the mixture was stirred for 3 hr. The reaction mixture was cooled to -78°C. An ether solution (80 ml) of 2-cyanopyrimidine (5.78 g) was added to the reaction mixture, and the mixture was stirred at -78°C for additional 4 hr. The reaction mixture was rendered weakly acidic by the addition of 10% hydrochloric acid, and the mixture was then stirred at room temperature for 30 min. The reaction mixture was neutralized with potassium carbonate. The organic layer was extracted with ethyl acetate, and the ethyl acetate layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an acetone-hexane system to give (5-methylfuran-2-yl)-(2-pyrimidyl)-methanone (3.2 g, yield 34%).

(5-Methylfuran-2-yl)-(2-pyrimidyl)-methanone (3.2 g), methanol (10 ml), and a 28% aqueous ammonia solution (20 ml) were placed in a sealed tube, and the mixture was stirred at 160°C overnight. The reaction mixture was cooled to room temperature, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography with a hexane-acetone system to give 6-methyl-2-pyrimidin-2-yl-pyridin-3-ol (1.32 g, yield 50%).

[0396] 4-Chloro-6,7-dimethoxy-quinoline (790 mg) and 6-methyl-2-pyrimidin-2-yl-pyridin-3-ol (660 mg) were dissolved in dimethylsulfoxide (4 ml), cesium carbonate (3.45 g) was

added to the solution, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The organic layer was extracted with chloroform, and the organic layer was then washed with saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a methanol-chloroform system and was further purified by thin layer chromatography with a methanol-chloroform system to give the title compound (438 mg, yield 33%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.76 (s, 3H), 4.02 (s, 3H), 4.05 (s, 3H), 6.46 (d, J = 5.4 Hz, 1H), 7.14 (t, J = 4.9 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.48 (s, 1H), 7.54 (s, 1H), 7.58 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 5.4 Hz, 1H), 8.66 (d, J = 4.9 Hz, 2H)

Mass spectrometric value (ESI-MS, m/z): 397 $(M+Na)^+$

[0397] Example 192: 2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethanol (compound 192)

To anhydrous tetrahydrofuran (100 ml) were added a 2.0 M lithium diisopropylamide/heptane, tetrahydrofuran, an ethylbenzene solution (26.2 ml), and tri-n-butyltin hydride (14.1 ml) in that order under an argon atmosphere at 0°C. The mixture was stirred at 0°C for 15 min. The reaction mixture was cooled to -78°C. 2-Chloropyrimidine (5.0 g) dissolved in anhydrous tetrahydrofuran (20 ml) was added dropwise to the cooled reaction mixture. The mixture was slowy brought to room temperature and was stirred overnight. Water was added to the reaction mixture to stop the reaction. The mixture was filtered through Celite, and the filtrate was extracted with ethyl acetate. The ethyl acetate layer was then washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-ethyl acetate system to give

2-tri-n-butylstannylpyrimidine (9.1 g, yield 56%).

2-Tri-n-butylstannylpyrimidine (5.0 g) was dissolved in tetrahydrofuran (130 ml) under an argon atmosphere. A 1.6 M n-butyllithium/hexane solution (8.6 ml) was added dropwise to the solution at -78°C, and the mixture was stirred at -78°C for 30 min. 4,5-Dimethylfurfural (1.85 g) dissolved in tetrahydrofuran (20 ml) was added dropwise to the solution, and the mixture was brourgh to room temperature with stirring. Water was added to the reaction mixture to stop the reaction. The solvent was removed by distillation under the reduced pressure, and water was added to the residue. The mixture was extracted with ethyl acetate, and the ethyl acetate layer was then washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a hexane-ethyl acetate system to give (5-ethylfuran-2-yl)-pyrimidin-2-yl-methanol (888 mg, yield 32%).

(5-Ethylfuran-2-yl)-pyrimidin-2-yl-methanol (880 mg) was dissolved in chloroform (15 ml), manganese dioxide (3.8 g) was added to the solution, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through Celite, and the solvent was removed from the filtrate by distillation under the reduced pressure. The residue was used in the next reaction without purification.

The residue, methanol (7 ml), and a 28% aqueous ammonia solution (8 ml) were placed in a sealed tube, and the mixture was stirred at 160°C overnight. The reaction mixture was cooled to room temperature, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography with a hexane-acetone system to give 6-ethyl-2-pyrimidin-2-yl-pyridin-3-ol (305 mg, yield 35%).

[0398] 6-Benzyloxy-4-chloro-quinoline (1.00 g), 6-ethyl-2-pyrimidin-2-yl-pyridin-3-ol(746 mg), and 4-dimethylaminopyridine (1.36 g) were dissolved in

dimethylsulfoxide (5 ml), cesium carbonate (3.62 g) was added to the solution, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The organic layer was extracted with chloroform, and the organic layer was then washed with saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a methanol-chloroform system and further purified by thin layer chromatography with a methanol-chloroform system to give 6-benzyloxy-4-(6-ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline (1.25 g, yield 77%).

6-Benzyloxy-4-(6-ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline (1.25 g) was dissolved in trifluoroacetic acid (7 ml). Methanesulfonic acid (0.7 ml) was added to the solution, and the mixture was stirred at 70°C for 2 hr. The reaction mixture was concentrated under the reduced pressure. Water was added to the reaction mixture, and the mixture was neutralized with an aqueous sodium hydrogencarbonate solution. The organic layer was extracted with chloroform, and the organic layer was then washed with saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give 4-(6-ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-ol (990 mg, yield 100%).

[0399]

4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-ol (990 mg) was dissolved in N,N-dimethylformamide (6 ml). Potassium carbonate (1.35 g) and 2-bromoethanol (0.7 ml) were added to the solution, and the mixture was stirred at 70°C overnight. The reaction mixture was concentrated under the reduced pressure. Water was added to the residue, and the orgnaic layer was extracted with chloroform. The organic layer

was then washed with saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with an acetone-chloroform system to give the title compound (789 mg, yield 71%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.41 (t, J = 7.8 Hz, 3H), 2.19 (m, 1H), 3.05 (q, J = 7.8 Hz, 2H), 4.04 (m, 2H), 4.22 (t, J = 4.2 Hz, 2H), 6.56 (d, J = 5.4 Hz, 1H), 7.14 (t, J = 4.9 Hz, 1H), 7.41 - 7.45 (m, 2H), 7.58 - 7.61 (m, 2H), 8.05 (d, J = 9.0 Hz, 1H), 8.48 (d, J = 5.4 Hz, 1H), 8.66 (d, J = 4.9 Hz, 2H)

Mass spectrometric value (ESI-MS, m/z): 411 $(M+Na)^+$

[0400] Example 200: 2-[4-(5,6-Dimethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethanol (compound 200)

2,3-Dimethylfuran (1.5 g) was dissolved in diethyl ether (20 ml) under an argon atmosphere. A 1.6 M n-butyllithium/hexane solution (10.9 ml) was added dropwise to the solution at 0°C, and the mixture was stirred under reflux for 2.5 hr. Thereafter, the reaction mixture was cooled to -78°C. 2-Cyanopyrimidine (1.8 g) dissolved in diethyl ether (8 ml) was added dropwise to the cooled reaction mixture, and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice to stop the reaction, was acidified with 1 M hydrochloric acid, and was extracted with ethyl acetate. The ethyl acetate layer was then washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-acetone system to give (4,5-dimethylfuran-2-yl)-(2-pyrimidyl)-methanone (226 mg, yield 7%).

(4,5-Dimethylfuran-2-yl)-(2-pyrimidyl)-methanone (220 mg), methanol (2 ml), and a 28% aqueous ammonia solution (2 ml) were placed in a sealed tube, and the mixture

was stirred at 160°C overnight. The reaction mixture was cooled to room temperature, and the solvent was then removed by distillation under the reduced pressure. The residue was purified by column chromatography with a hexane-acetone system to give 5,6-dimethyl-2-pyrimidin-2-yl-pyridin-3-ol (129 mg, yield 59%).

[0401] 6-Benzyloxy-4-chloro-quinoline (1.30 g) and 5,6-dimethyl-2-pyrimidin-2-yl-pyridin-3-ol (1.46 g) were dissolved in dimethylsulfoxide (15 ml), cesium carbonate (4.71 g) was added thereto, and the mixture was stirred at 130°C overnight. The reaction mixture was cooled to room temperature. Water was then added to the reaction mixture, and the organic layer was extracted with ethyl acetate. The ethyl acetate layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an acetone-hexane system to give 6-benzyloxy-4-(5,6-dimethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline (1.52 g, yield 73%).

6-Benzyloxy-4-(5,6-dimethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline (773 mg) was dissolved in trifluoroacetic acid (3 ml). Methanesulfonic acid (0.3 ml) was added to the solution, and the mixture was stirred at room temperature for 4 hr. Water was added to the reaction mixture, and the mixture was neutralized with an aqueous sodium hydrogencarbonate solution. The organic layer was extracted with ethyl acetate, and the ethyl acetate layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was washed with diethyl ether to give 4-(5,6-dimethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-ol (467 mg, yield 76%).

[0402]

4-(5,6-Dimethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-

quinolin-6-ol (439 mg) was dissolved in N,N-dimethylformamide (5 ml). Potassium carbonate (0.89 g) and 2-bromoethanol (0.27 ml) were added to the solution, and the mixture was stirred at 80°C for 5.5 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (159 mg, yield 32%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.69 (s, 3H), 4.03 (t, J = 4.4 Hz, 2H), 4.23 (t, J = 4.9 Hz, 2H), 6.49 (d, J = 5.2 Hz, 1H), 7.10(t, J = 4.9 Hz, 1H), 7.38 - 7.41 (m, 2H), 7.60 (d, J = 3.0 Hz, 1H), 7.96 (d, J = 9.3 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.65 (d, J = 4.9 Hz, 2H)

Mass spectrometric value (ESI-MS, m/z): 411 $(M+Na)^+$

[0403] Example 202: 2-[4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethanol (compound 202)

6-Benzyloxy-4-chloro-quinoline (2.73 g), 6-methyl-2-pyrimidin-2-yl-pyridin-3-ol(949 mg), and cesium carbonate (4.96 g) were suspended in dimethylsulfoxide (25 ml), and the suspension was stirred at 130°C overnight. The reaction mixture was cooled to room temperature, and water was added thereto. The mixture was extracted with chloroform, and the chloroform layer was washed with saturated brine and was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a chloroform-methanol system to give 6-benzyloxy-4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline (1.64 g, yield 77%).

6-Benzyloxy-4-(6-methyl-2-pyrimidin-2-yl-pyridin-3

-yloxy)-quinoline (1.64 g) was dissolved in trifluoroacetic acid (30 ml). Methanesulfonic acid (2.5 ml) was added to the solution, and the solution was stirred at 80°C for one hr. Water was added to the reaction mixture, the mixture was neutralized with an aqueous sodium hydrogencarbonate solution, and the organic layer was extracted with chloroform. The chloroform layer was washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure to give 4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-ol (1.28 g, yield 99%).

[0404]

4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-ol (1.10 g) was dissolved in N,N-dimethylformamide (10 ml). Potassium carbonate (1.85 g), N,N,N,N-tetrabutylammonium iodide (124 mg), and 2-bromoethanol (1.47 g) were added to the solution, and the mixture was stirred at 40°C for 20 hr. The solvent was removed by distillation under the reduced pressure. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was dried over anhydrous magnesium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with a methanol-chloroform system to give the title compound (745 mg, yield 59%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.74 (s, 3H), 4.03(t, J = 4.4 Hz, 2H), 4.21(t, J = 4.4 Hz, 2H), 6.50 (d, J = 5.2 Hz, 1H), 7.12(t, J = 4.8 Hz, 1H), 7.36 (dd, J = 9.6, 2.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 2.8 Hz, 1H), 7.94 (d, J = 9.6 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.66 (d, J = 4.8 Hz, 2H)

Mass spectrometric value (ESI-MS, m/z): 397 $(M+Na)^+$

[0405] Example 205: 2-[4-(6-Methyl-[2,2']bipyridyl-3-yloxy)-quinolin-6-yloxy]-ethanol (compound 205)

6-Iodo-2-picolin-5-ol (10.0 g) was dissolved in N,N-dimethylformamide (100 ml). Benzyl bromide (7.50 g) and potassium carbonate (17.6 g) were added to the solution, and the mixture was stirred at room temperature for 6 hr. The reaction mixture was filtered, water was added to the filtrate, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water and was dried over sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was used in the next reaction without purification.

The residue and dichlorobis(triphenylphosphine)-palladium(II) (1.50 g) were dissolved in anhydrous tetrahydrofuran (200 ml) under an argon atmosphere. A 0.5 M 2-pyridylzinc bromide/tetrahydrofuran solution (100 ml) was added to the solution, and the mixture was stirred under reflux overnight. The reaction mixture was cooled to room temperature, and the solvent was removed by distillation under the reduced pressure. A 1 N sodium hydroxide solution was added to the residue, and the mixture was extracted with chloroform. The chloroform layer was washed with water and was then dried over sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was used in the next reaction without purification.

Trifluoroacetic acid (40 ml) and methanesulfonic acid (2 ml) were added to the residue, and the mixture was stirred at 100°C overnight. The reaction mixture was cooled to room temperature, and the solvent was removed by distillation under the reduced pressure. The residue was neutralized with a saturated aqueous sodium bicarbonate solution and was then filtered. The filtrate was extracted with ethyl acetate, and the ethyl acetate layer was washed with water and was extracted with 1 N hydrochloric acid. The aqueous layer was washed with ethyl acetate and was then neutralized by the addition of a saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate, was washed with water

and was dried over sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography with a hexane-ethyl acetate system to give 6-methyl-[2,2′]bipyridyl-3-ol (5.09 g, yield 64%) (3 steps).

[0406] 4-Benzyloxy-phenylamine hydrochloride (1.18 g) and 5-methoxymethylene-2,2-dimethyl-[1,3]dioxan-4,6-dione (1.03 g) were suspended in 2-propanol (15 ml). Triethylamine (0.78 ml) was added to the suspension, and the mixture was stirred at 70°C for 3 hr. The reaction mixture was cooled to room temperature, was filtered and was washed with ether. The residue as such was used in the next reaction without purification.

The residue and biphenyl (4.34 g) were suspended in diphenyl ether (12 ml), and the suspension was stirred at 240°C overnight. The reaction mixture was cooled to room temperature, and the cooled reaction mixture as such was applied to column chromatography with a methanol-chloroform system. The crude product as such was used in the next reaction without further purification.

The crude product was suspended in diisopropylethylamine (3 ml), phosphorus oxychloride (0.5 ml) was added to the suspension, and the mixture was stirred at 120°C for 3hr. Water was added to the reaction mixture under ice cooling. The aqueous layer was neutralized with an aqueous sodium hydrogencarbonate solution, and the organic layer was extracted with ethyl acetate. The ethyl acetate layer was then washed with water and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography with an ethyl acetate-hexane system to give 6-benzyloxy-4-chloro-quinoline (147 mg, yield 10%) (3 steps).

[0407] Anhydrous dimethylsulfoxide (25 ml) was added to 6-methyl-[2,2′]bipyridyl-3-ol (2.00 g), 6-benzyloxy-4-chloroquinoline (5.79 g), and cesium carbonate (7.00 g), and the mixture was stirred at 130°C overnight. The

reaction mixture was cooled to room temperature. Water was added to the cooled reaction mixture, and the mixture was extracted with chloroform. The chloroform layer was washed with water and was dried over sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography with a hexane-acetone system to give 3-(6-benzyloxy-quinolin-4-yloxy)-6-methyl-[2,2′]bipyridyl (3.38 g, yield 75%).

Trifluoroacetic acid (10 ml) and methanesulfonic acid (0.5 ml were added to 3-(6-benzyloxy-quinolin-4-yloxy)-6-methyl-[2,2′]bipyridyl (3.36 g), and the mixture was stirred under reflux for 6 hr. The solvent was removed by distillation under the reduced pressure. The residue was neturatlized by the addition of a saturated aqueous sodium bicarbonate solution. Chloroform was added thereto, and the resultant precipitate was collected by filtration and was washed with water and chloroform to give crystals. The filtrate was subjected to separation, and the chloroform layer was washed with water and was then dried over sodium sulfate. The solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography with a chloroform-methanol system. The purified product was combined with the above crystals to give 4-(6-methyl-[2,2′]bipyridyl-3-yloxy)-quinolin-6-ol (2.42 g, yield 92%).

[0408] N,N-Dimethylformamide (40 ml) was added to 4-(6-methyl-[2,2′]bipyridyl-3-yloxy)-quinolin-6-ol (2.42 g), potassium carbonate (3.05 g), and 2-bromoethanol (2.76 g), and the mixture was stirred at 60°C overnight. The reaction mixture was cooled to room temperature, water was added to the cooled mixture, and the mixture was extracted with ethyl acetate. The ethyl acetate layer was dried over sodium sulfate, and the solvent was removed by distillation under the reduced pressure. The residue was purified by column chromatography with a chloroform-methanol system to give the title compound

(1.19 g, yield 43%).

[1]H-NMR ($CDCl_3$, 400 MHz): δ 2.33(bs, 1H), 2.73 (s, 3H), 4.04 (m, 2H), 4.23 (t, J = 4.2 Hz, 2H), 6.45 (d, J = 5.1 Hz, 1H), 7.14 (dd, J = 7.6, 4.9 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.40 (dd, J = 2.7, 9.3 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.57 - 7.65 (m, 2H), 7.80 (d, J = 7.3 Hz, 1H), 7.96 (d, J = 9.3 Hz, 1H), 8.46 (d, J = 5.1 Hz, 1H), 8.52 (m, J = 4.6 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 374 $(M+1)^+$

[0409] <u>Example 206: 2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethyl acetate (compound 206)</u>

2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethanol (compound 192) (210 mg) was dissolved in dichloromethane (5 ml). Triethylamine (0.75 ml) and acetic anhydride (0.15 ml) were added to the solution under ice cooling, and the mixture was stirred at room temperature for 3 hr. Water was added to the reaction mixture, and the mixture was neutralized with an aqueous sodium hydrogencarbonate solution. The organic layer was extracted with ethyl acetate, and the organic layer was then washed with saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by thin layer chromatography with a methanol-chloroform system to give the title compound (202 mg, yield 87%).

[1]H-NMR ($CDCl_3$, 400 MHz): δ 1.41 (t, J = 7.8 Hz, 3H), 2.12 (s, 3H), 3.04 (q, J = 7.6 Hz, 2H), 4.31 (t, J = 4.9 Hz, 2H), 4.49 (t, J = 4.9 Hz, 2H), 6.52 (d, J = 5.1 Hz, 1H), 7.13 (t, J = 4.9 Hz, 1H), 7.38 - 7.44 (m, 2H), 7.56 - 7.59 (m, 2H), 7.96 (d, J = 9.3 Hz, 1H), 8.48 (d, J = 5.1 Hz, 1H), 8.67 (d, J = 4.9 Hz, 2H)

Mass spectrometric value (ESI-MS, m/z): 453 $(M+Na)^+$

[0410] <u>Example 209: 4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-6-(2-morpholin-4</u>

-yl-ethoxy)-quinoline (compound 209)

4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-ol (1.03 g) was dissolved in N,N-dimethylformamide (15 ml). Potassium carbonate (1.60 g) and 2-bromo-1-chloroethane (1.5 ml) were added to the solution, and the mixture was stirred at 65°C overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography on silica gel with an ethyl acetate-hexane system to give 6-(2-chloro-ethoxy)-4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline as a crude product (741 mg).

A part (103 mg) of the crude product was dissolved in N,N-dimethylformamide (2 ml). Potassium carbonate (240 mg) and morpholine (0.2 ml) were added to the solution, and the mixture was stirred at 80°C overnight. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed by distillation under the reduced pressure, and the residue was purified by column chromatography on silica gel with an acetone-chloroform system to give the title compound (24 mg, yield 12%) (2 steps).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.60 - 2.62 (m, 4H), 2.76 (s, 3H), 2.87 (t, J = 5.6 Hz, 2H), 3.73 - 3.75 (m, 4H), 4.24 (t, J = 5.6 Hz, 2H), 6.50 (d, J = 5.4 Hz, 1H), 7.13 (t, J = 4.9 Hz, 1H), 7.37 - 7.41 (m, 2H), 7.54 - 7.57 (m, 2H), 7.94 (d, J = 9.3 Hz, 1H), 8.46 (d, J = 5.2 Hz, 1H), 8.67 (d, J = 4.9 Hz, 2H)

Mass spectrometric value (ESI-MS, m/z): 466 $(M+Na)^+$

[0411] Reference Examples

Synthesis schemes and Synthesis Examples of quinoline derivatives or quinazoline derivatives, that is,

compounds r1 to r469, having structures close to those of the compounds according to the present invention will be described.

Typical Synthesis Examples in each of the following shemes will be described. Other compounds in each of the schemes could easily be produced by a person having ordinary skill in the art according to the procedure of each scheme and the description of typical Synthesis Examples in each of the schemes.

[0412] Reference Production Example 1 shows a production example of intermediate r1 in scheme r3. Reference Production Example 2 shows a production examples of intermediate r2 in scheme r4. Reference Production Examples 3 and 4 show production examples of intermediates r3 and r4 in scheme r5.

[0413] <u>Reference Production Example 1: 2-[(6,7-Dimethoxy-4-quinolyl)oxy]-5-methylbenzaldehyde (intermediate r1)</u>

4-Chloro-6,7-dimethoxyquinoline (113 mg), 2-hydroxy-5-methylbenzaldehyde (344 mg), and 4-dimethylaminopyridine (313 mg) were suspended in o-dichlorobenzene (5 ml), and the suspension was stirred at 160°C for 2 hr. The reaction mixture was cooled to room temperature, and the solvent was then removed from the reaction mixture by distillation under the reduced pressure. Chloroform was added to the residue. The organic layer was washed with a 1 N aqueous sodium hydroxide solution and saturated brine and was dried over anhydrous magnesium sulfate. The solvent was removed from the reaction mixture by distillation under the reduced pressure. The residue was purified by column chromatography with a chloroform system to give the title compound (157 mg, yield 96%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.46 (s, 3H), 4.06 (s, 3H), 4.06 (s, 3H), 6.44 (d, J = 5.1 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 7.45 (s, 1H), 7.49 (m, 1H), 7.57 (s, 1H), 7.83 (d, J = 1.9 Hz, 1H), 8.51 (d, J = 1.5 Hz, 1H), 10.28 (s, 1H)

Mass spectrometric value (ESI-MS, m/z): 324 $(M+1)^+$

[0414] Reference Production Example 2: 2-(6,7-Dimethoxyquinolin-4-yloxy)-5-methoxybenzoic acid (intermediate r2)

Ethyl 2-(6,7-dimethoxyquinolin-4-yloxy)-5-methoxy-benzoate (143 mg) and lithium hydroxide (78 mg) were suspended in a mixed solvent composed of ethanol (10 ml) and water (1 ml), and the suspension was stirred at room temperature overnight. Next, the solvent was removed from the reaction mixture by distillation under the reduced pressure. Water was added to the residue, and the mixture was neutralized with 12 N hydrochloric acid. The mixture was then extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed from the extract by distillation under the reduced pressure to give the title compound (140 mg, yield 100%).

^{1}H-NMR ($CDCl_3$-d_1, 400 MHz): δ 3.73 (s, 3H), 3.80 (s, 3H), 3.95 (s, 3H), 6.44 (d, J = 5.6 Hz, 1H), 6.91 - 7.19 (m, 3H), 7.34 (s, 1H), 7.46 (s, 1H), 7.60 (s, 1H), 8.10 (d, J = 5.6 Hz, 1H), 13.26 (brs, 1H),

Mass spectrometric value (ESI-MS, m/z): 356 (M^++1)

[0415] Reference Production Example 3: [2-(7-Benzyloxy-6-methoxyquinolin-4-yloxy)-5-methoxyphenyl] ethanone (intermediate r3)

7-Benzyloxy-4-chloro-6-methoxyquinoline (3.00 mg), 5-methoxy-2-acetophenone (6.7 g), and 4-dimethylaminopyridine (4.9 g) were suspended in o-dichlorobenzene (30 ml), and the suspension was stirred at 180°C for 2 hr. The reaction mixture was cooled to room temperature. Water was added to the cooled reaction mixture, and the mixture was extracted with chloroform. The chloroform layer was washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was

removed from the reaction mixture by distillation under the reduced pressure. The residue was purified by thin layer chromatography with an acetone-hexane system to give the title compound (2.53 g, yield 59%).
^{1}H-NMR ($CDCl_3$-d_1, 400 MHz): δ 2.42 (s, 3H), 3.82 (s, 3H), 3.98 (s, 3H), 5.26 (s, 2H), 6.28 (d, J = 5.6 Hz, 1H), 7.03 - 7.08 (m, 1H), 7.23 - 7.51 (m, 9H), 8.39 (d, J = 5.6 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 430 (M^++1)

[0416] Reference Production Example 4: [2-(7-Hydroxy-6-methoxyquinolin-4-yloxy)-5-methoxyphenyl]ethanone (intermediate r4)

[2-(7-Benzyloxy-6-methoxyquinolin-4-yloxy)-5-methoxy-phenyl]ethanone (intermediate r3) (2.52 g) was suspended in a mixed solvent composed of methanesulfonic acid (3.0 ml) and trifluoroacetic acid (50 ml), and the suspension was stirred at 70°C for 0.5 hr. The solvent was removed from the reaction mixture by distillation under the reduced pressure. Water was added to the residue, and the mixture was neutralized with a sodium hydrogencarbonate powder. The mixture was then extracted with chloroform. The chloroform layer was then washed with water and saturated brine and was dried over anhydrous sodium sulfate. The solvent was removed from the reaction mixture by distillation under the reduced pressure. The residue was purified by column chromatography with an acetone-hexane system to give the title compound (1.23 g, yield 62%).
^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.50 (s, 3H), 3.91 (s, 3H), 4.00 (s, 3H), 6.35 (d, J = 5.2 Hz, 1H), 7.34 (m, 3H), 7.42 (s, 1H), 7.61 (s, 1H), 8.44 (d, J = 5.2 Hz, 1H), 10.24 (brs, 1H),
Mass spectrometric value (ESI-MS, m/z): 338 (M^+-1)

[0417] Production of compounds of Reference Examples

Compounds according to the present invention and compounds close thereto were produced.

The relationship between the produced compounds and the schemes applied to the production of the compounds is as shown in the following table.

[0418] Table r-1:

Scheme	Compound
r2:	r1 to r5, r12, r13, r15 to r17, r19, r22, r24, r26 to r42, r57, r62 to r72, r74, r75, r77, r78, r161, r162 and r425
r3:	r9 to r11, r18, r43 to 56, r58 to 61, r73, r166, r172, r181, r188 to r192, r293, r306 to r311 and r418 to r420
r4:	r79 to r114
r5:	r118 to r160, r312 to r409 and r440 to r469
r6:	r163
r7:	r7 and r8
r8:	r6
r9:	r14
r10:	r20 and r21
r11:	r23
r12:	r76, r165, r173, r174 and r182 to r187
r13:	r115 to r117, r202, r203, r205, r206, r208 to r210, r214, r215, r217 to r221, r275 and r276

[0419] Table r-2:

Scheme	Compound
r14:	r164, r167 to r171, r294 to r296, r298 and r302
r15:	r175 to r180
r16:	r200 and r201
r17:	r204, r222 and r280
r18:	r207
r19:	r211, r212, r216, r223 to r255, r259, r261 to r267, r291, r434 and r438
r20:	r213

r21: r256 to r258
r22: r277
r23: r278 and r279
r24: r281, r282, r284 and r287 to r289
r25: r283, r285, r286, r290, r292, r421 to r424, r426 to r428, r436, and r439
r26: r297
r27: r299
r28: r300
r29: r301, r303 and r304
r30: r305
r31: r410 to r414
r32: r415 to r417
r33: r193 to r199
r34: r260, r268 to r274, r429 to r433, r435 and r437

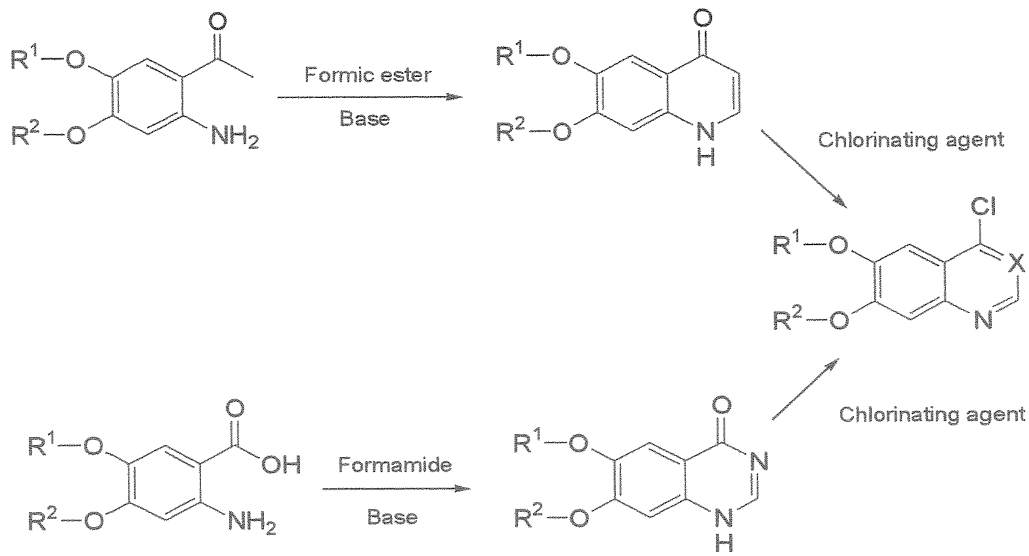
[0420] Production schemes

A certain group of compounds related to the compounds according to the present invention can be produced according to the following schemes r1 to r34.

In the description of production schemes r1 to r34 in the following Reference Examples, symbols of substituents such as R1 and R2 are used. Despite the definition in the description other than Reference Examples in the present specification, the symbols of the substituents means as defined in the Reference Examples.

[0421] Scheme r1:

[Chemical formula 39]



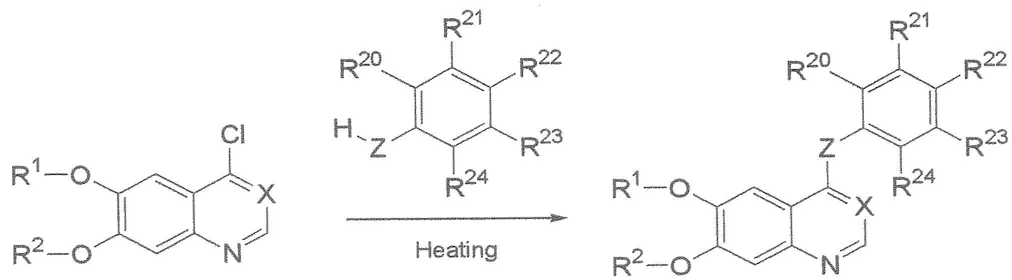
wherein X represents CH or N, and

R^1 and R^2 independently may represent group $-OR^X$ wherein R^X represents a hydrogen atom or $-(CH_2)m-R^{aX}$. R^{aX} represents a hydrogen atom, a halogen atom, hydroxyl, a saturated or unsaturated three- to six-membered carbocyclic or heterocyclic group, C1-4 alkoxy, C1-4 alkoxycarbonyl, or $-NR^{bX}R^{cX}$. R^{bx} and R^{cx}, which may be the same or different, represent a hydrogen atom or C1-6 alkyl wherein the C1-6 alkyl group is optionally substituted by hydroxyl, an oxygen atom, amino, a nitrogen atom, or C1-4 alkyl. R^{bX} and R^{cX} together may combine with the nitrogen atom to which they are attached to form a saturated or unsaturated five- or six-membered heterocyclic group. This heterocyclic group may further contain one or more heteroatoms. The heterocyclic group is optionally substituted by C1-4 alkyl optionally substituted by hydroxyl; hydroxyl; an oxygen atom; aminocarbonyl; C1-4 alkoxy; C1-4 alkoxycarbonyl; or a saturated or unsaturated five- or six-membered heterocyclic group. Further, the heterocyclic group may condense with another saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group to form a bicyclic group. m is an integer of 1 to 6. The alkyl chain part $-(CH_2)m-$ in the group $-(CH_2)m-R^{aX}$ is optionally substituted by hydroxy; an oxygen atom; $-OR^{dX}$ wherein R^{dX} represents C1-4 alkyl or C1-4 alkylcarbonyl; or C1-4 alkyl optionally

substituted by hydroxyl or a halogen atom.

[0422] Scheme r2:

[Chemical formula 40]

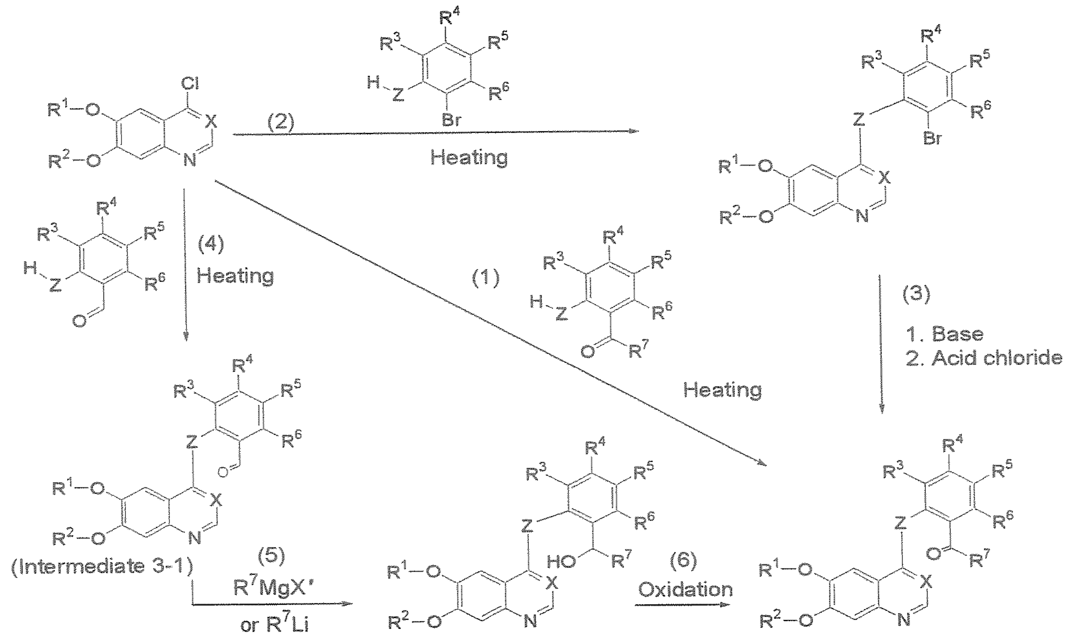


wherein Z represents -O-, -NH-, -S-, or -C(=O)-, and R^{20} to R^{24}, which may be the same or different, represent a hydrogen atom, a halogen atom, C1-10 alkyl, C1-8 alkoxy, C2-6 alkenyl, phenylcarbonyl, amino, nitro, or a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group. R^{20} and R^{21}, or R^{23} and R^{24} together may combine with the carbon atoms to which they are attached represent a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group. The other substituents are as defined in other production schemes in other Reference Examples.

[0423] The aimed compounds, i.e., 4-phenoxyquinoline derivatives, 4-anilinoquinoline derivatives, or corresponding quinazoline derivatives can be synthesized by reacting a phenol derivative or a corresponding aniline derivative with a 4-chloroquinoline derivative or a corresponding quinazoline derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C. In scheme r1, phosphoryl chloride may be mentioned as the chlorinating agent.

[0424] Scheme r3:

[Chemical formula 41]



wherein X′ represents a halogen atom,

R^3 to R^6, which may be the same or different, represent a hydrogen atom, hydroxyl, a halogen atom, C1-6 alkyl, C1-10 alkoxy, C2-6 alkenylcarbonyloxy, C1-4 alkylcarbonyl, C1-4 alkylthio, or phenyl, and R^3 and R^4, R^4 and R^5, and R^5 and R^6 together may combine with the carbon atoms to which they are attached represent a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group,

R^7 represents a hydrogen atom, C1-8 alkyl, C2-6 alkenyl, a saturated or an unsaturated five- or six-membered carbocyclic or heterocyclic group, group -O-R^8, or group -N(-R^9)R^{10} wherein R^8, R^9 and R^{10}, and R^{11} and R^{12} represent C1-10 alkyl, C2-8 alkenyl, or a saturated or unsaturated five- or six-membered carbocyclic group or the like, and

the other substituents are as defined in other production schemes in other Reference Examples.

[0425] In this scheme, the aimed compounds can be synthesized through any of the following three routes (i) to (iii).

(i) The aimed compounds can be synthesized by reacting a 4-chloroquinoline derivative or a corresponding quinazoline derivative with a phenol derivative or a corresponding aniline derivative in a suitable solvent, for

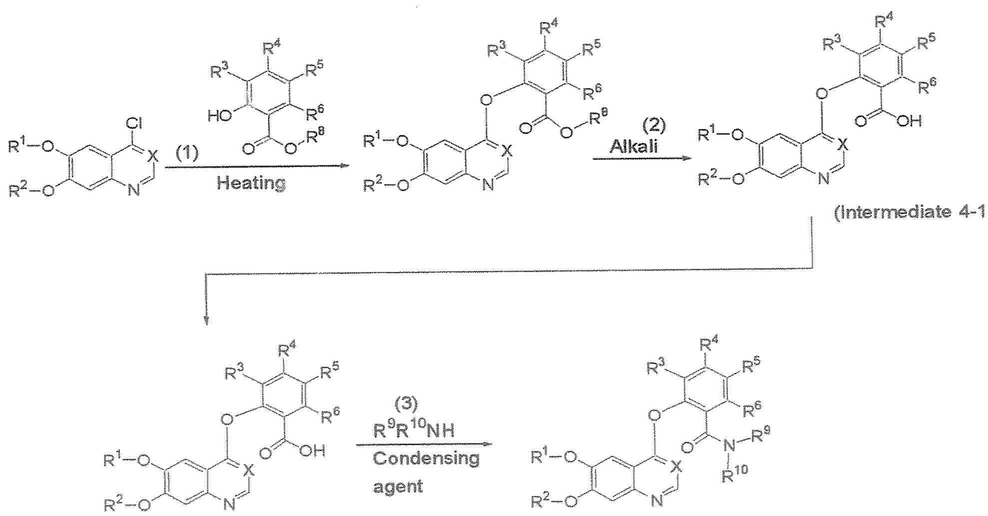
example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (1)).

(ii) The aimed compounds can be synthesized by reacting a 4-chloroquinoline derivative or a corresponding quinazoline derivative with an o-bromophenol derivative or a corresponding o-bromoaniline derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (2)), subjecting the bromo site to dipole inversion with a metal base, for example, n-butyllithium, and reacting the resultant anion with an acid chloride (step (3)).

(iii) The aimed compounds can be produced by reacting a 4-chloroquinoline derivative or a corresponding quinazoline derivative with an o-hydroxybenzaldehyde derivative or a corresponding o-aminobenzaldehyde derivartive in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (4)), then reacting the resultant compound with an alkylating agent, for example, methylmagnesium bromide (step (5)), and oxidizing the resultant alcohol (step (6)).

[0426] Scheme r4:

[Chemical formula 42]



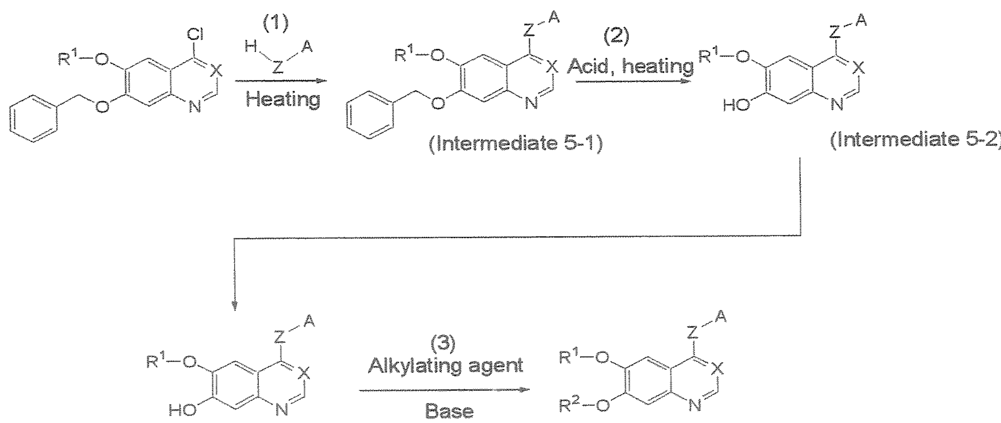
wherein the substituents are as defined above.

[0427] The aimed ester-type compounds can be produced

by reacting a 4-chloroquinoline derivative or a corresponding quinazoline derivative with an o-hydroxybezoic ester derivative or a corresponding o-aminobenzoic ester derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (1)). Next, the aimed compounds can be synthesized by hydrolyzing the ester-type compound with an alkali (step (2)) and reacting the amine with a condensing agent, for example, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (step (3)).

[0428] Scheme r5:

[Chemical formula 43]



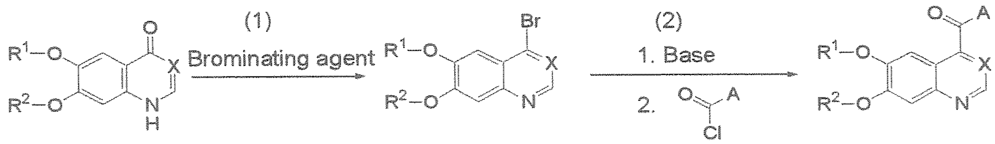
wherein A is as defined in the portions other than the Reference Examples in the present specification, and

the other substituents are as defined above.

[0429] A 7-benzyloxy-4-chloroquinoline derivative or a corresponding quinazoline derivative is provided and is reacted with a phenol derivative or a corresponding aniline derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (1)). The aimed compounds can be synthesized by deprotecting the resultant intermediate 5-1, that is, removing the benzyl group, with an acid (step (2)) and reacting the resultant intermediate 5-2 with an alkylating agent, for example, 1-bromo-2-chloroethane, in the presence of a base (step (3)).

[0430] Scheme r6:

[Chemical formula 44]

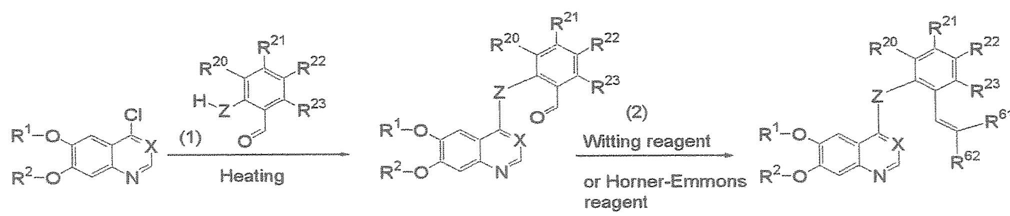


wherein the substituents are as defined above.

[0431] The aimed compounds can be produced by providing a 4-quinolone derivative or a corresponding quinazolone derivative, reacting this compound with a brominating agent, for example, phosphoryl bromide (step (1)), then subjecting the bromo site to dipole inversion with a metal base, for example, n-butyllithium, and reacting the resultant anion with an acid chloride (step (2)).

[0432] Scheme r7:

[Chemical formula 45]

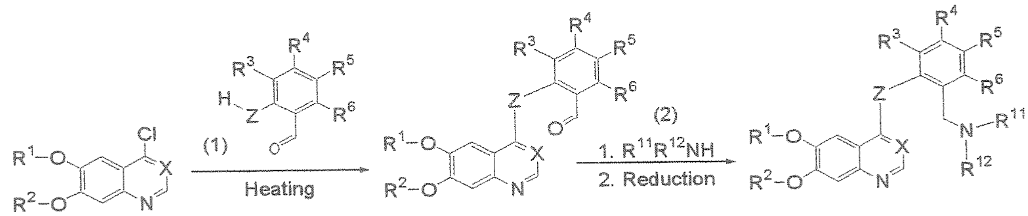


wherein R^{61} and R^{62}, which may be the same or different, represent a hydrogen atom, C1-4 alkyl, C1-4 alkoxy, C1-4 alkoxycarbonyl, or phenyl, and the substituents are as defined above.

[0433] The aimed compounds can be synthesized by reacting a 4-chloroquinoline derivative or a corresponding quinazoline derivative with an o-hydroxybenzaldehyde derivative or a corresponding o-aminobenzaldehyde derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (1)) and then reacting the resultant compound with a Witting reagent or a Horner-Emmons reagent (step (2)). Phosphorus ylide may be mentioned as these reagents.

[0434] Scheme r8:

[Chemical formula 46]

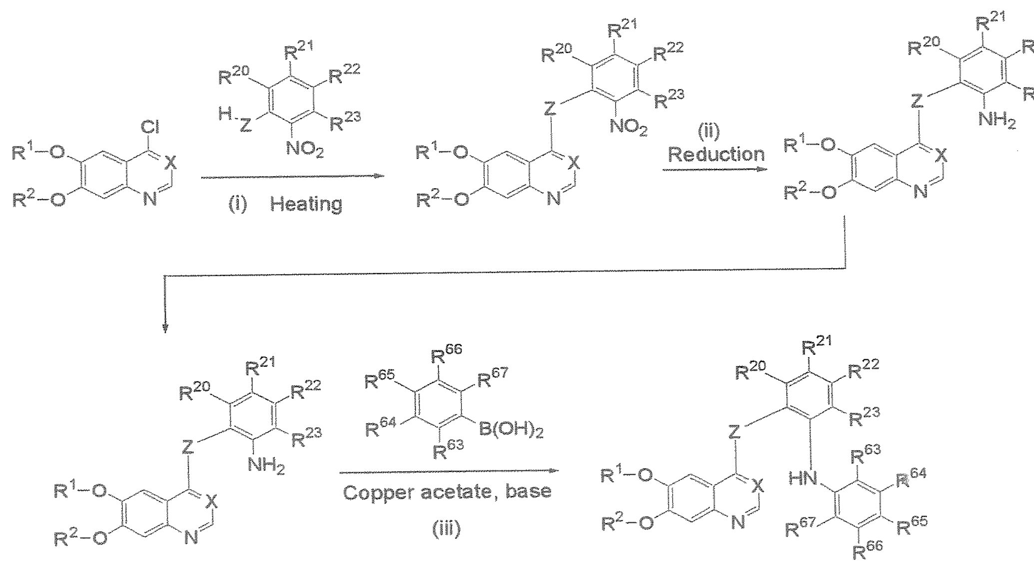


wherein the substituents are as defined above.

[0435] The aimed compounds can be produced by reacting a 4-chloroquinoline derivative or a corresponding quinazoline derivative with an o-hydroxybenzaldehyde derivative or a corresponding o-aminobenzaldehyde derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (1)), then reacting the resultant compound with an amine ($R^{11}R^{12}NH$) to give an imine, and then reducing the imine (step (2)).

[0436] Scheme r9:

[Chemical formula 47]



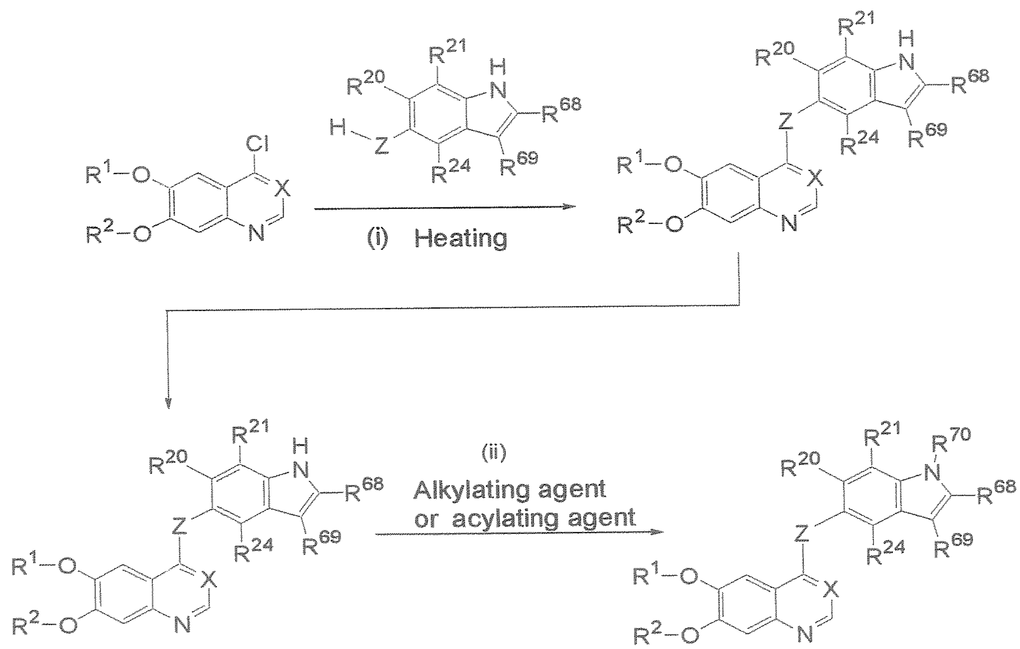
wherein R^{63} to R^{67}, which may be the same or different, represent a hydrogen atom, hydroxyl, a halogen atom, or C_{1-4} alkyl, and the other substituents are as defined above.

[0437] The aimed compounds can be synthesized by reacting a 4-chloroquinoline derivative or a corresponding

quinazoline derivative with an o-nitrophenol derivative or a corresponding o-nitroaniline derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (i)), then reducing the nitro group (step (ii)), and reacting the resultant compound with a phenylboronic acid derivative (step (iii)).

[0438] Scheme r10:

[Chemical formula 48]

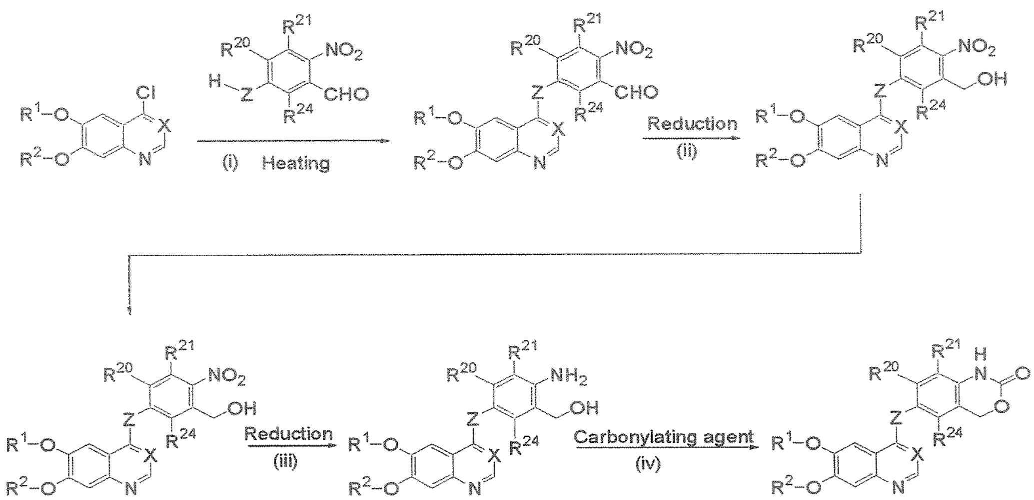


wherein R^{68} to R^{70}, which may be the same or different, represent a hydrogen atom, a halogen atom, C_{1-2} alkylcarbonyl, C_{1-2} alkoxycarbonyl, or C_{1-4} alkyl, and the other substituents are as defined above.

[0439] The aimed compounds can be synthesized by reacting a 4-chloroquinoline derivative or a corresponding quinazoline derivative with a 5-hydroxyindole derivative or a corresponding 5-aminoindole derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (i)) and then alkylating the amino group with an alkylating agent, for example, methyl iodide, or acylating the amino group with an acylating agent, for example, acetyl chloride (step (ii)).

[0440] Scheme r11:

[Chemical formula 49]

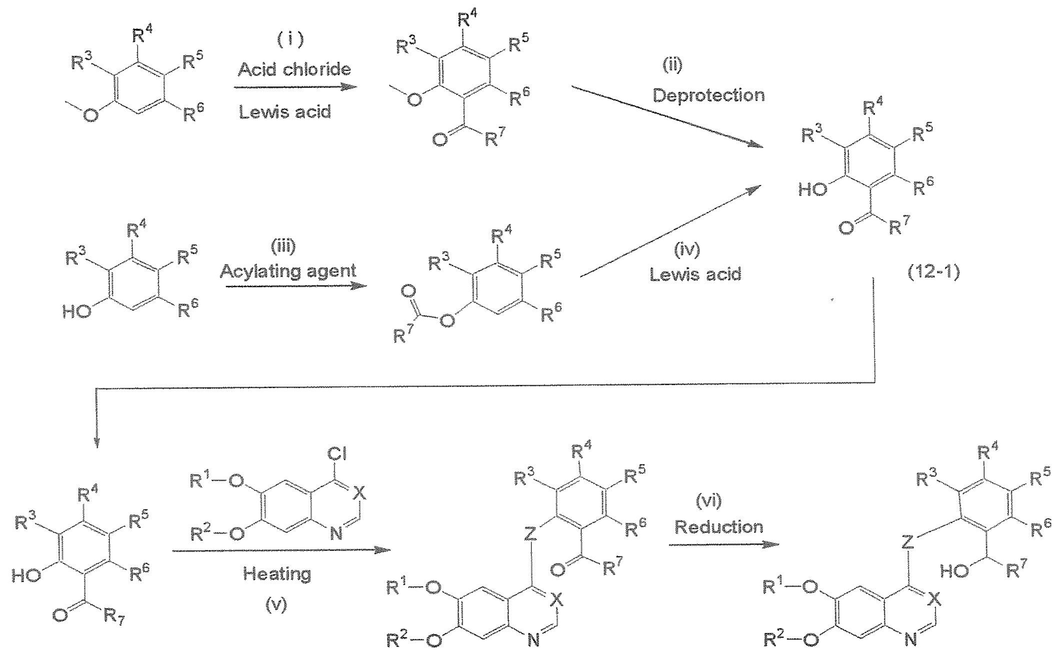


wherein the substituents are as defined above.

[0441] The aimed compounds can be synthesized by reacting a 4-chloroquinoline derivative or a corresponding quinazoline derivative with a 3-hydroxy-6-nitrobenzaldehyde derivative or a corresponding 5-amino-2-nitrobenzaldehyde derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent (step (i)), reducing the formyl group (step (ii)), then reducing the nitro group in the resultant compound (step (iii)), and reacting the resultant compound with a carbonylation agent, for example, triphosgene (step (iv)).

[0442] Scheme r12:

[Chemical formula 50]



wherein the substituents are as defined above.

[0443] The compounds of formula (12-1) can be produced by reacting an anisole derivative with an acid chloride in the presence of a Lewis acid (step (i)) and deprotecting the resultant compound, that is, removing the methoxy group (step (ii)).

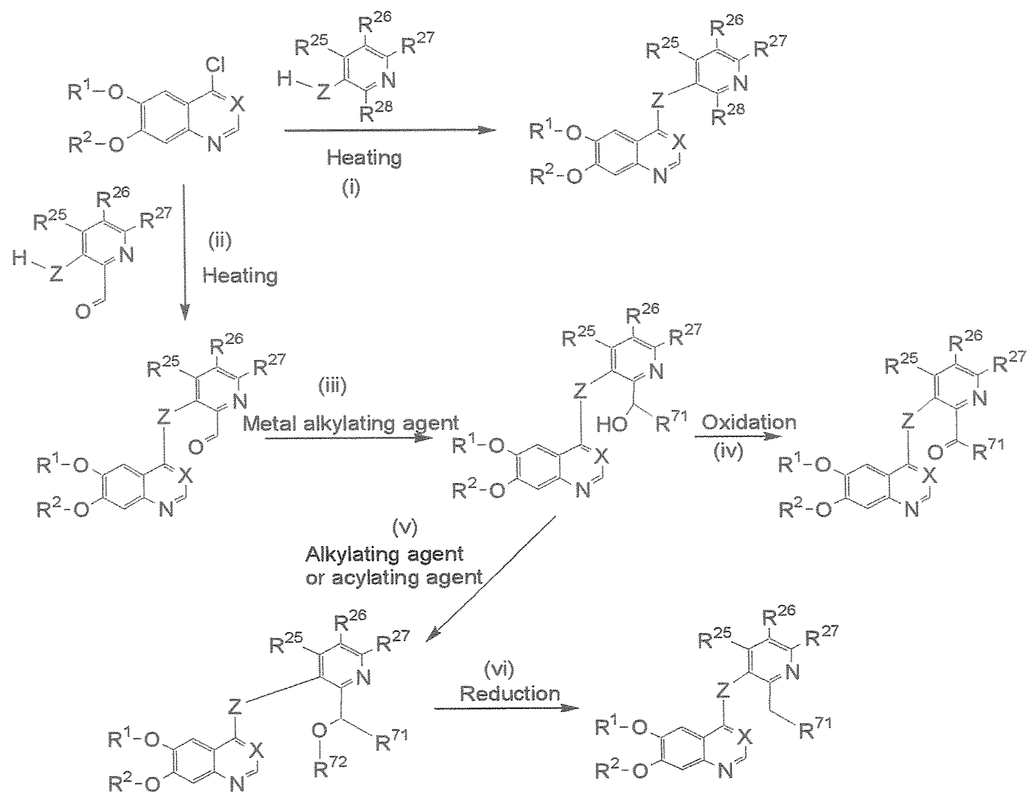
Alternatively, the compounds of formula (12-1) can be produced by acylating a phenol derivative with an acylating agent, for example, acetyl chloride or acetic anhydride (step (iii)) and then reacting the resultant compound with a Lewis acid, for example, scandium trifluoromethanesulfonate (step (iv)).

A aimed compound, for example, compound r76, can be synthesized by reacting the compound of formula (12-1) with a 4-chloroquinoline derivative or a corresponding quinazoline derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (v)).

Further, a aimed compound, for example, compound r165, can be synthesized by reducing the acyl group in the resultant compound (step (vi)).

[0444] Scheme r13:

[Chemical formula 51]



wherein R^{25} to R^{27}, which may be the same or different, represent a hydrogen atom, a halogen atom, C1-6 alkyl, C1-8 alkoxy, C1-4 alkylcarbonyl, C1-4 alkylthio, or phenylcarbonyl, and R^{25} and R^{26}, and R^{26} and R^{27} together may combine with the carbon atoms to which they are attached represent a saturated or unsaturated five- or six-membered carbocyclic or heterocyclic group,

R^{28} represents a hydrogen atom, a halogen atom, nitro group, cyano group, C1-6 alkyl, C1-8 alkoxy, C1-4 alkylcarbonyl, C2-6 alkenyl, C2-6 alkynyl, a saturated or unsaturated three- to eight-membered carbocyclic oxy, a saturated or unsaturated six-membered carbocyclic carbonyl or heterocyclic carbonyl, or a saturated or unsaturated three- to eight-membered carbocyclic or heterocyclic group,

R^{71} represents methyl, ethyl, phenyl, or 2-pyridyl,

R^{72} represents a hydrogen atom or methylcarbonyl,

and

the other substituents are as defined above.

[0445] The aimed compounds can be synthesized by reacting a 4-chloroquinoline derivative or a corresponding quinazoline derivative with a 3-hydroxypyridine derivative or a corresponding 3-aminopyridine derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (i)).

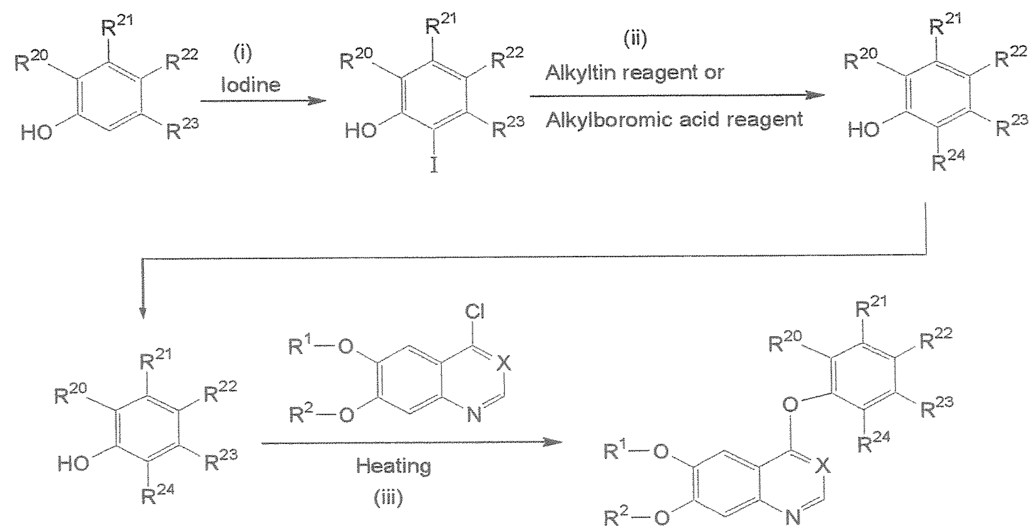
Alternatively, a 4-chloroquinoline derivative or a corresponding quinazoline derivative is reacted with a 3-hydroxy-2-pyridine carbaldehyde derivative or a corresponding 3-amino-2-pyridine carbaldehyde derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (ii)), and the resultant compound is then reacted with an alkylating agent, for example, methylmagnesium bromide (step (iii)).

A aimed compound, for example, compound r117, can be then synthesized by oxidizing the resultant alcoholic compound, for example, with manganese dioxide as an oxidizing agent (step (iv)).

Alternatively, another aimed compound, for example, compound r218, can be synthesized by alkylating the hydroxyl group in the resultant alcoholic compound with an alkylating agent, for example, methyl iodide or ethyl iodide, or by acylating the hydroxyl group in the resultant alcoholic compound with an acylating agent, for example, acetyl chloride or acetic anhydride (step (v)). A further aimed compound, for example, compound r214, can be synthesized by reducing this compound, for example, with a hydrogen gas/palladium hydroxide as a reducing agent (step (vi)).

[0446] <u>Scheme r14:</u>

[Chemical formula 52]

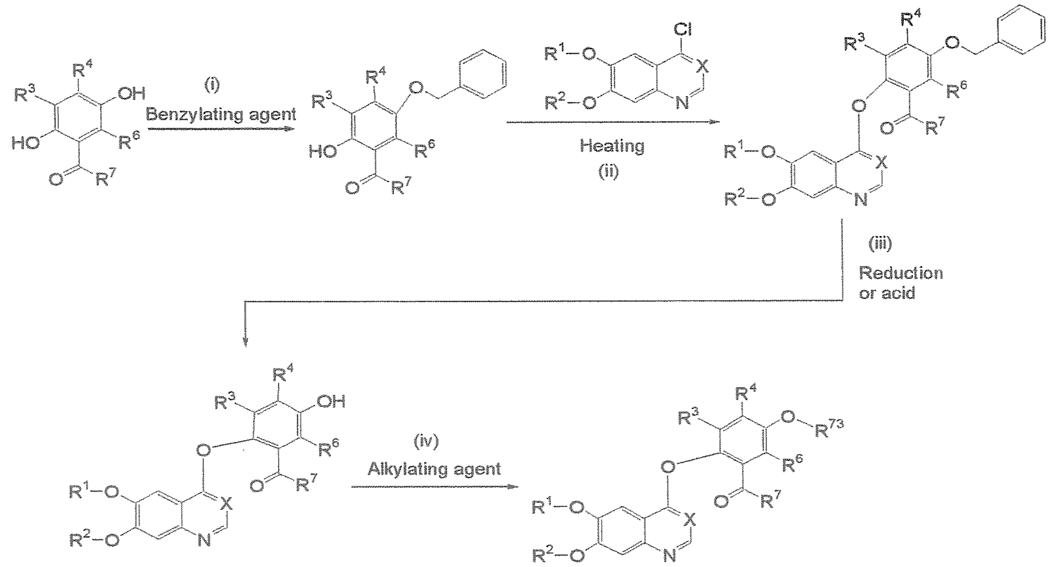


wherein the substituents are as defined above.

[0447] The aimed compounds can be produced by reacting a phenol derivative with iodine (step (i)), reacting the allyl iodide with an alkyltin reagent, for example, tri-n-butyl-(2-pyridyl)-tin, or an alkylboronic acid reagent, for example, 3-pyridylboronic acid, in the presence of a suitable transition metal catalyst, for example, tetrakistriphenylphosphine palladium (step (ii)), and reacting the phenol derivative thus obtained with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (iii)).

[0448] <u>Scheme r15:</u>

[Chemical formula 53]



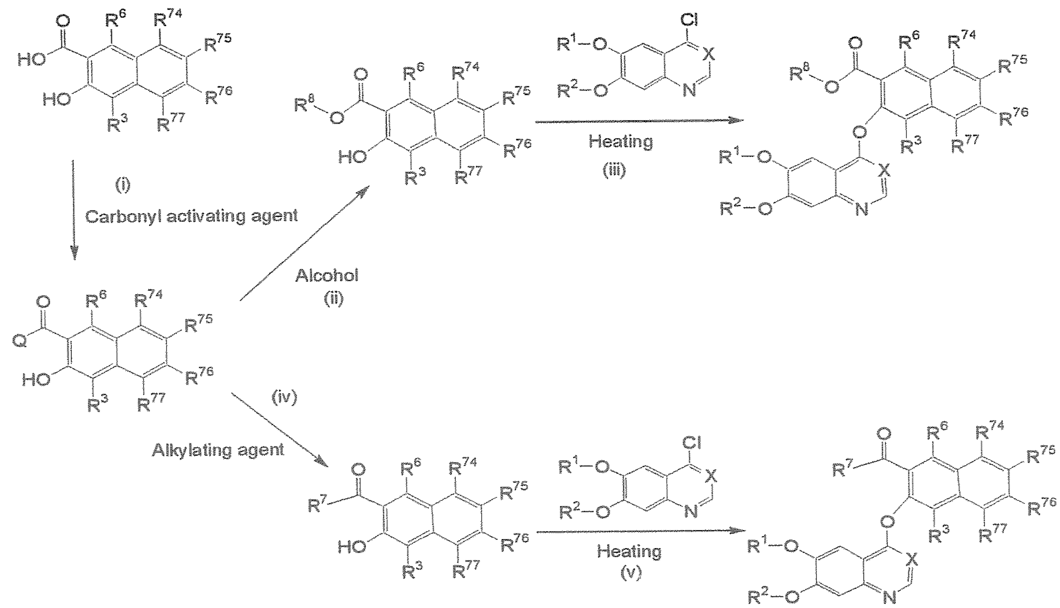
wherein R^{73} represents a hydrogen atom, or C_{1-4} alkyl optionally substituted by phenyl, and

the other substituents are as defined above.

[0449] The aimed compounds can be produced by reacting a 2,5-dihydroxyphenyl ketone derivative with a benzylating agent, for example, benzyl bromide (step (i)), reacting the monophenol derivative thus obtained with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (ii), deprotecting the resultant compound, that is, removing the benzyl group in the resultant compound, with a suitable acid, for example, methanesulfonic acid/trifluoroacetic acid, or by reductiing agent (step (iii)), and then alkylating the phenolic hydroxyl in the resultant compound with an alkylating agent, for example, ethyl iodide (step (iv)).

[0450] Scheme r16:

[Chemical formula 54]



wherein R^{74} to R^{77} represent a hydrogen atom, a halogen atom, hydroxyl, or C_{1-4} alkyl, Q represents, for example, chlorine or N,O-dimethylhydroxyamine, and the other substituents are as defined above.

[0451] In this scheme, the aimed compounds can be synthesized through the following two routes.

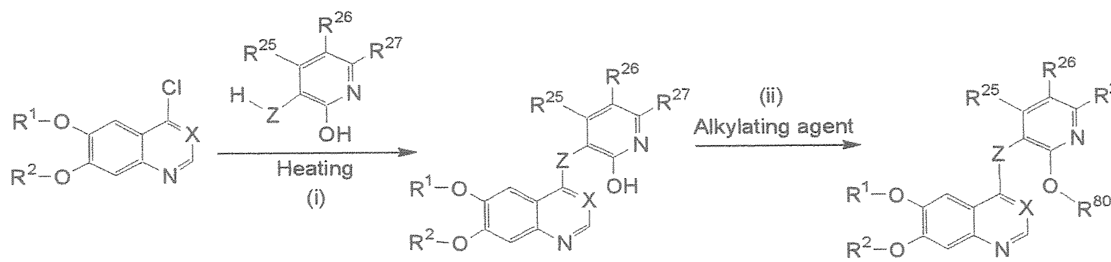
(I) The comtemplated compound can be produced by reacting a hydroxynaphthalenecarboxylic acid derivative with a suitable carbonyl activating agent, for example, thionyl chloride (step (i)), then reacting the active carboxylic acid derivative thus obtained with an alcohol (step (ii)) to give an ester derivative, then reacting the ester derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (iii)).

(II) The aimed compounds can be produced by reacting the active carboxylic acid derivative produced in step (i) with an alkylating agent, for example, methylmagnesium bromide (step (iv)) to give a ketone derivative and then reacting the ketone derivative with a 4- chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the

absence of a solvent, for example, at 120 to 180°C (step (v)).

[0452] Scheme r17:

[Chemical formula 55]



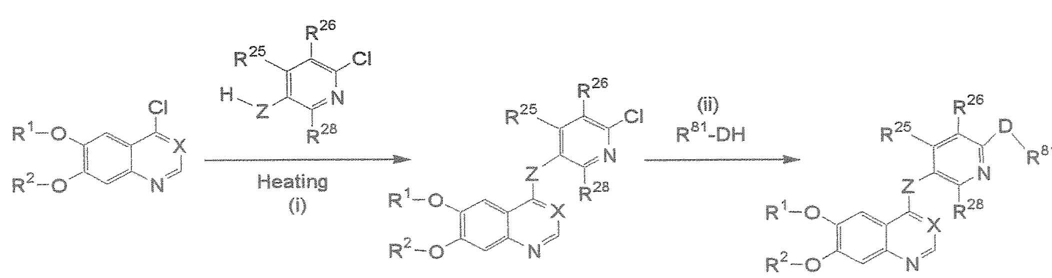
wherein R^{80} represents cyclopentyl, cyclohexyl, or phenyl, and

the other substituents are as defined above.

[0453] The aimed compounds can be produced by reacting a 2-hydroxypyridine derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (i)) and then alkylating the resultant compound with an alkylating agent, for example, ethyl iodide (step (ii)).

[0454] Scheme r18:

[Chemical formula 56]



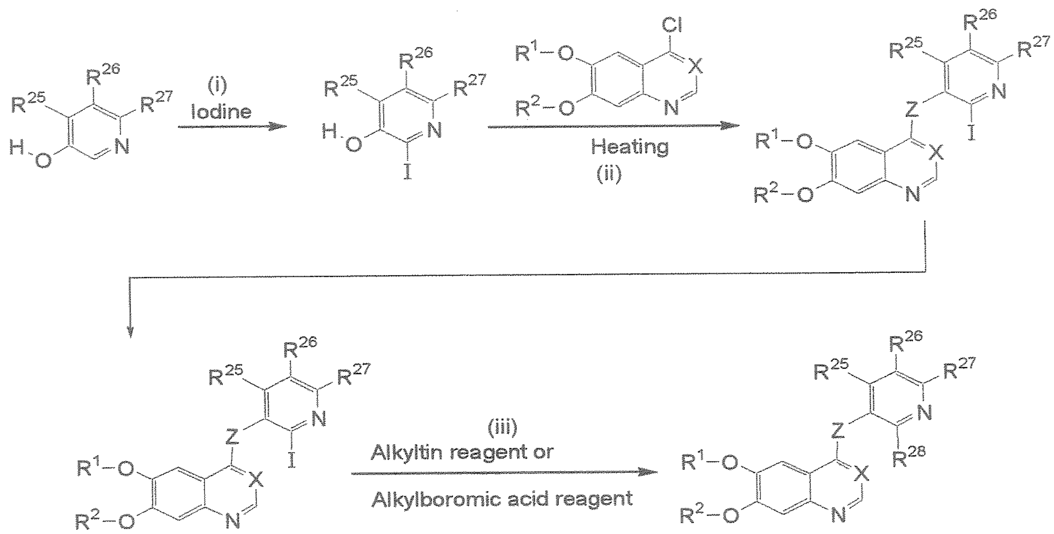
wherein R^{81} represents a hydrogen atom or C_{1-4} alkyl, D represents an oxygen atom, a nitrogen atom, or a sulfur atom, and the other substituents are as defined above.

[0455] The aimed compounds can be produced by reacting a 2-chloropyridine derivative with a 4-chloroquinoline

derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (i)) and reacting the resultant compound with a nucleophilic reagent, for example, methanol (step (ii)).

[0456] Scheme r19:

[Chemical formula 57]

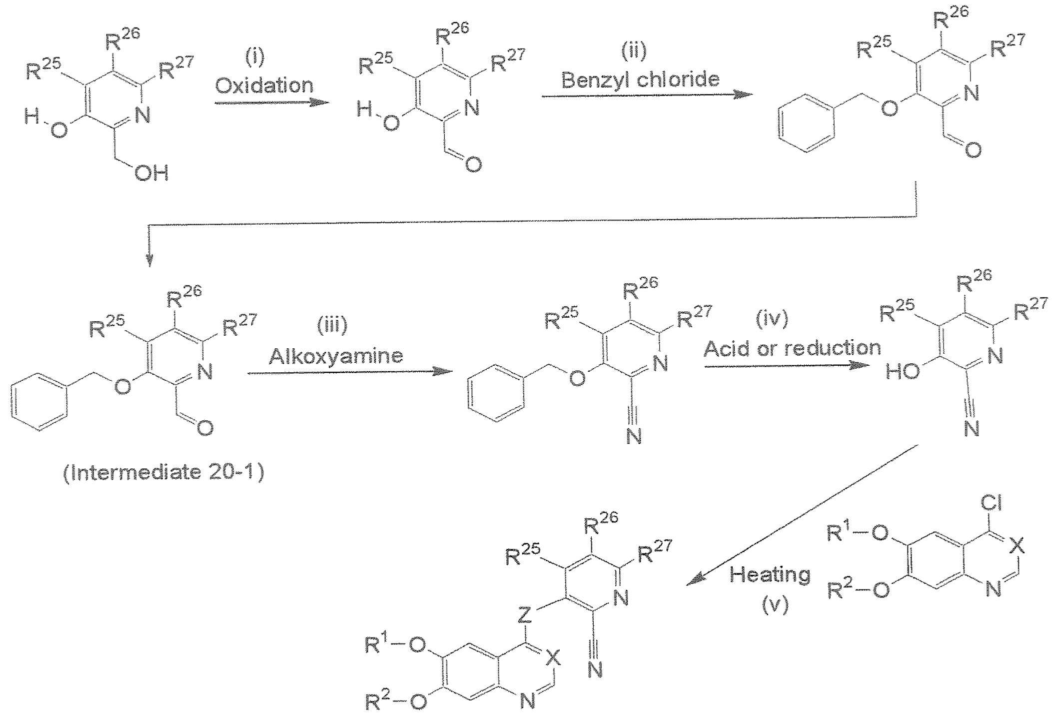


wherein the substituents are as defined above.

[0457] The aimed compounds can be produced by reacting a 3-hydroxypyridine derivative with iodine in a suitable solvent, for example, methanol (step (i)), reacting the 2-iodopyridine derivative thus obtained with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (ii)), then reacting the resultant compound with an alkyltin reagent, for example, tri-n-butyl-(2-pyridyl)-tin, or an alkylboronic acid reagent, for example, 3-pyridylboronic acid, in the presence of a suitable transition metal catalyst, for example, tetrakistriphenylphosphine palladium (step (iii)).

[0458] Scheme r20:

[Chemical formula 58]



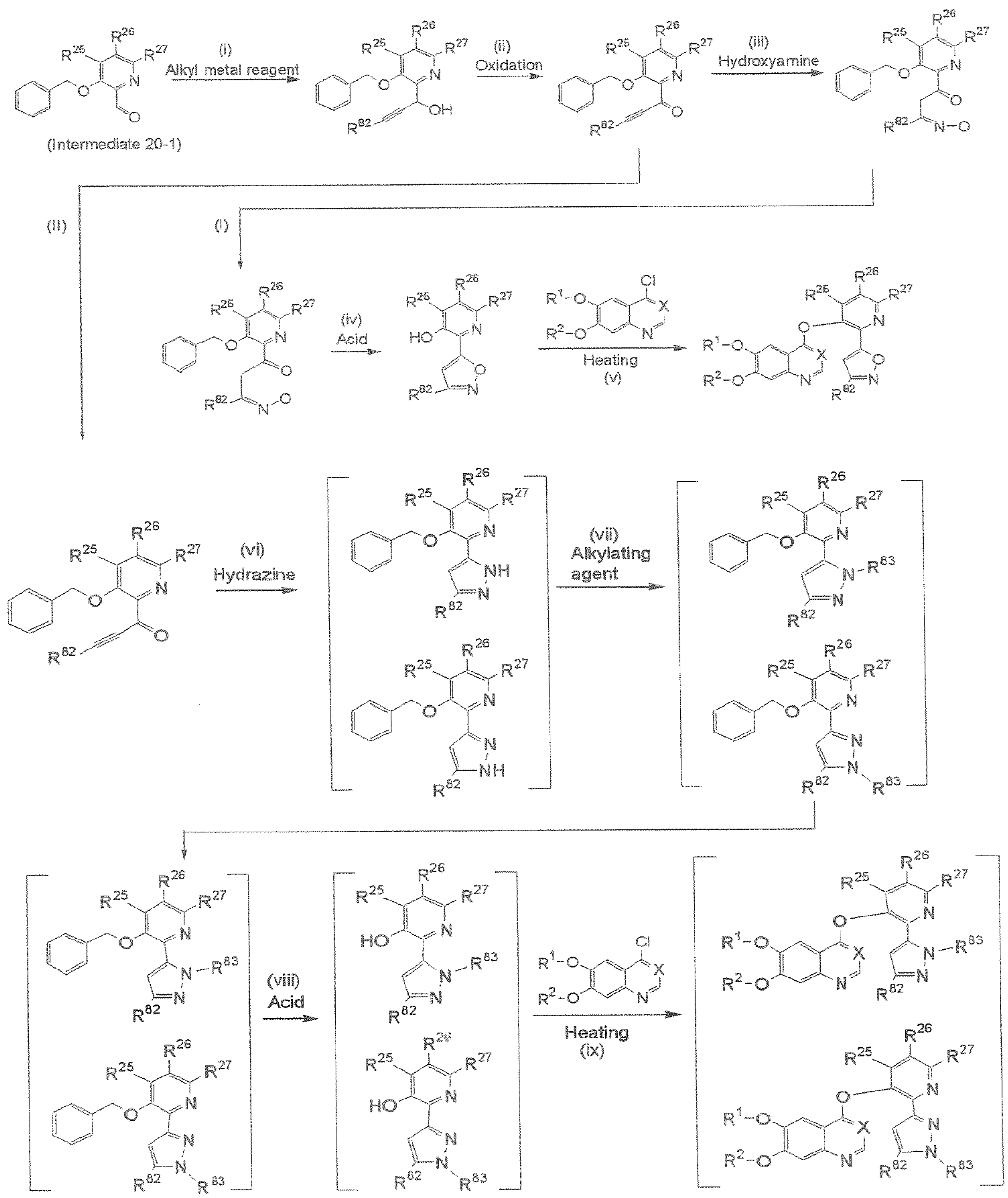
(Intermediate 20-1)

wherein the substituents are as defined above.

[0459] Intermediate 20-1 can be produced by reacting the above starting compound with a suitable oxidizing agent, for example, manganese dioxide (step (i)) and then reacting the remaining hydroxy group in the resultant compound with a suitable benzylating agent, for example, benzyl chloride (step (ii)). Next, a corresponding cyanopyridine derivative can be produced by reacting intermediate 20-1 with an alkoxyamine (step (iii)). The aimed compounds can be produced by deprotecting the cyanopyridine derivative thus obtained with a suitable acid, for example, methanesulfonic acid/trifluoroacetic acid, or a suitable reducing agent, for example, a hydrogen gas/palladium hydroxide (step (iv)), and then reacting the resultant hydroxypyridine derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (v)).

[0460] Scheme r21:

[Chemical formula 59]



wherein R^{82} and R^{83} represent hydroxyl; cyano; a halogen atom; C1-4 alkoxy; phenyloxy; C1-4 alkylcarbonyl; amino optionally substituted by C1-4 alkyl or C1-4 alkylcarbonyl; aminocarbonyl optionally substituted by C1-4 alkyl; or C1-4 alkyl optionally substituted by hydroxyl or a halogen atom, and

the other substituents are as defined above.

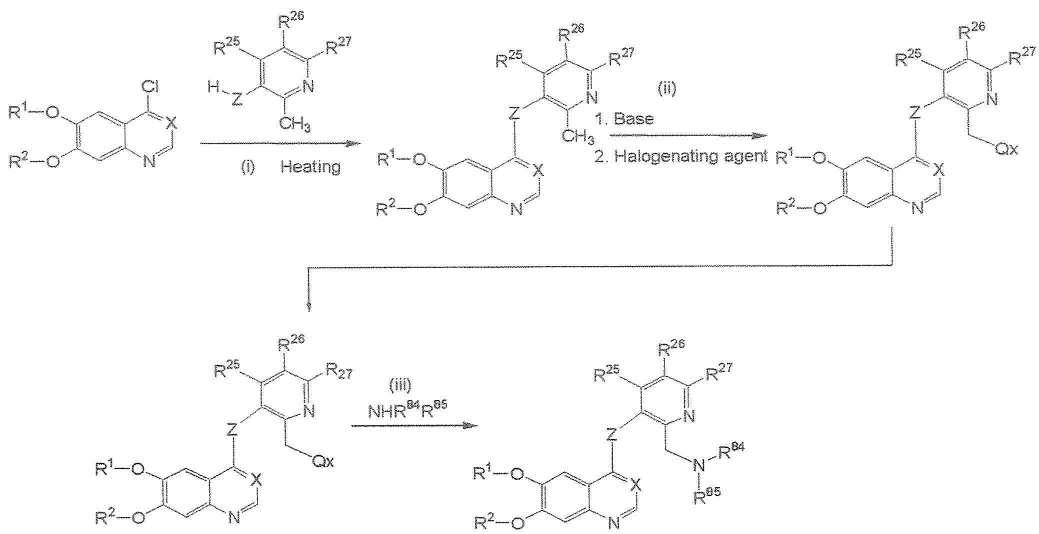
[0461] In this scheme, the aimed compounds can be synthesized through the following two routes.

(I) The aimed compounds can be produced by reacting intermediate 20-1 produced according to scheme r20 with an alkyne metal reagent, for example, 1-propynylmagnesium bromide (step (i)), then oxidizing the hydroxyl group in the resultant compound with a suitable oxidizing agent, for example, a benzyl group (step (ii)) to give a ketone derivative, reacting the ketone derivative with hydroxyamine (step (iii)), reacting the resultant compound with a suitable acid, for example, methanesulfonic acid/trifluoroacetic acid (step (iv)) to give a 3-hydroxy-2-isoxazoylpyridine derivative, and then reacting the 3-hydroxy-2-isoxazoylpyridine derivative thus obtained with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (v)).

[0462] (II) The aimed compounds can be produced by reacting intermediate 20-1 produced according to scheme r20 with an alkyne metal reagent, for example, 1-propynylmagnesium bromide (step (i)), then oxidizing the hydroxyl group in the resultant compound with a suitable oxidizing agent, for example, a benzyl group (step (ii)) to give a ketone derivative, reacting the ketone derivative with hydrazine (step (vi)), reacting the resultant compound with an alkylating agent, for example, methyl iodide (step (vii)) to give an N-alkylpyrazole derivative, reacting the N-alkylpyrazole derivative with a suitable acid, for example, methanesulfonic acid/trifluoroacetic acid (step (viii)) to give a 3-hydroxypyridine derivative, and then reacting the 3-hydroxypyridine derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (ix)).

[0463] Scheme r22:

[Chemical formula 60]

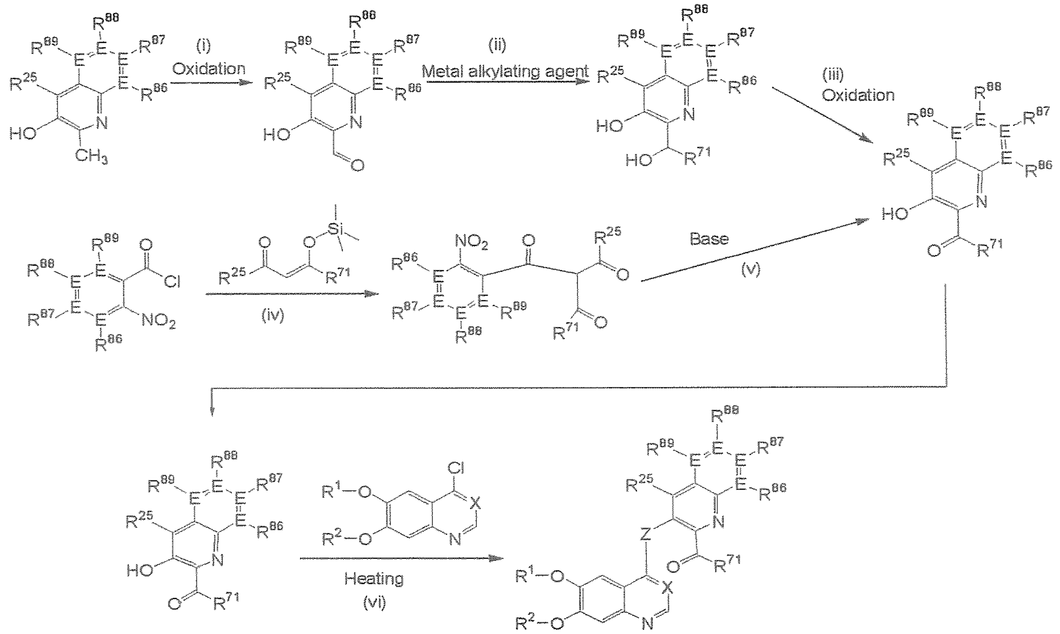


wherein Qx represents a halogen atom, preferably a chlorine atom or a bromine atom, and the other substituents are as defined above.

[0464] The aimed compounds can be produced by reacting a 3-hydroxy-2-methylpyridine derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (i)) to give a quinoline derivative, allowing a suitable base, for example, lithium diisopropylamide, to act on the resultant compound to produce carbanion, reacting the carbanion with a halogenating agent, for example, N-bromosucciimide (step (ii)), and then reacting the resultant compound with an amine (step (iii)).

[0465] Scheme r23:

[Chemical formula 61]



wherein at least one of E's represents a heteroatom such as a nitrogen atom while the other E's represent a carbon atom, or all of E`s represent a carbon atom,

R^{86} to R^{89} represent a hydrogen atom, a halogen atom, or C_{1-4} alkyl, and

the other substituents are as defined above.

[0466] In this scheme, the aimed compounds can be synthesized through the following two routes.

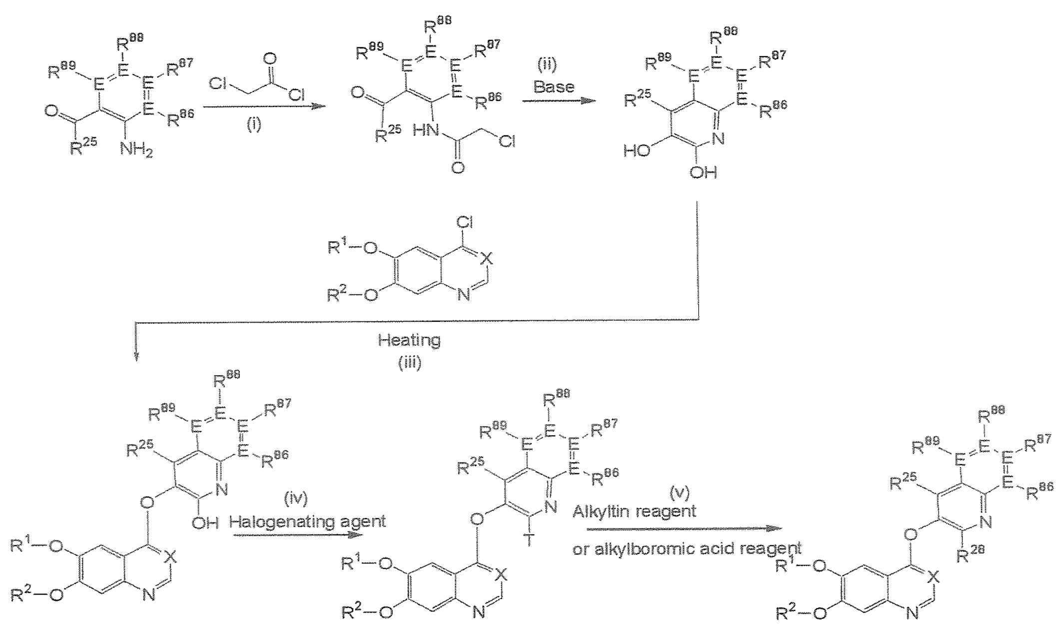
(I) The aimed compounds can be produced by reacting a 3-hydroxy-2-methylquinoline derivative with a suitable oxidizing agent, for example, selenium dioxide (step (i)), reacting the aldehyde derivative with a metal alkylating agent, for example, methylmagnesium bromide (step (ii)), then oxidizing the resultant alcoholic compound with a suitable oxidizing agent, for example, manganese dioxide (step (iii)) to give a ketone derivative, and reacting the ketone derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (vi)).

[0467] (II) The aimed compounds can be produced by reacting an acid chloride derivative with silyl enol ether, for

example, 4-trimethylsilanyloxy-penta-3-en-2-one) (step (iv)), reacting the ketone derivative thus obtained with a suitable base, for example, an aqueous potassium hydroxide solution (step (v)) to give a 3-hydroxyquinoline derivative, and reacting the resultant 3-hydroxyquinoline derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (vi)).

[0468] Scheme r24:

[Chemical formula 62]



wherein at least one of E's represents a heteroatom such as a nitrogen atom while the other E's represent a carbon atom, or all of E`s represent a carbon atom,

T represents a halogen atom, preferably a bromine atom, and

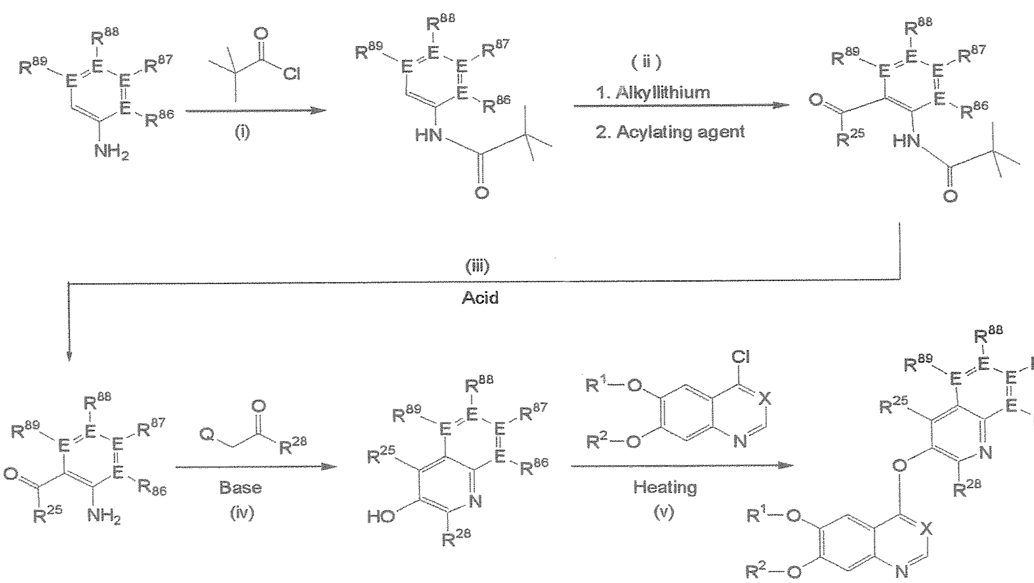
the other substituents are as defined above.

[0469] The aimed compounds can be produced by reacting an aniline derivative with chloroacetyl chloride (step (i)), then reacting the resultant amide derivative with a suitable

base, for example, an aqueous potassium hydroxide solution (step (ii)) to give a 2,3-dihydroxyquinoline derivative, reacting the 2,3-dihydroxyquinoline derivative thus obtained with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (iii)) to give a 2-hydroxyquinoline derivative, reacting the 2-hydroxyquinoline derivative with a suitable halogenating agent, for example, tetrabutylammonium bromide (step (iv)) to give a 2-haloquinoline derivative, and reacting the 2-haloquinoline derivative with an alkyltin reagent , for example, tri-n-butyl-(2-pyridyl)-tin, or an alkylboronic acid reagent, for example, 3-pyridylboronic acid in the presence of a suitable transition metal catalyst, for example, tetrakistriphenylphosphine palladium (step (v)).

[0470] Scheme r25:

[Chemical formula 63]

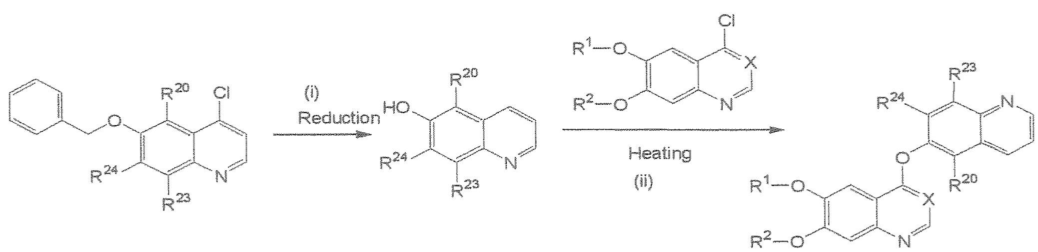


wherein at least one of E's represents a heteroatom such as a nitrogen atom while the other E's represent a carbon atom, or all of E`s represent a carbon atom, and the other substituents in the scheme are as defined above.

[0471] The aimed compounds can be produced by reacting an aniline derivative with pivaloyl chloride (step (i)) to give an amide derivative, then reacting the amide derivative thus obtained with a suitable alkyllithium, for example, n-butyllithium, reacting the resultant anion with an acylating agent, for example, N,N-dimethylformamide (step (ii)), removing the pivaloyl group with a suitable acid, for example, hydrochloric acid (step (iii)) to give an o-acylaniline derivative, reacting the resultant o-acylaniline derivative with a methyl ketone derivative (step (iv)), and then reacting the resultant 3-hydroxyquinoline derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (v)).

[0472] Scheme r26:

[Chemical formula 64]

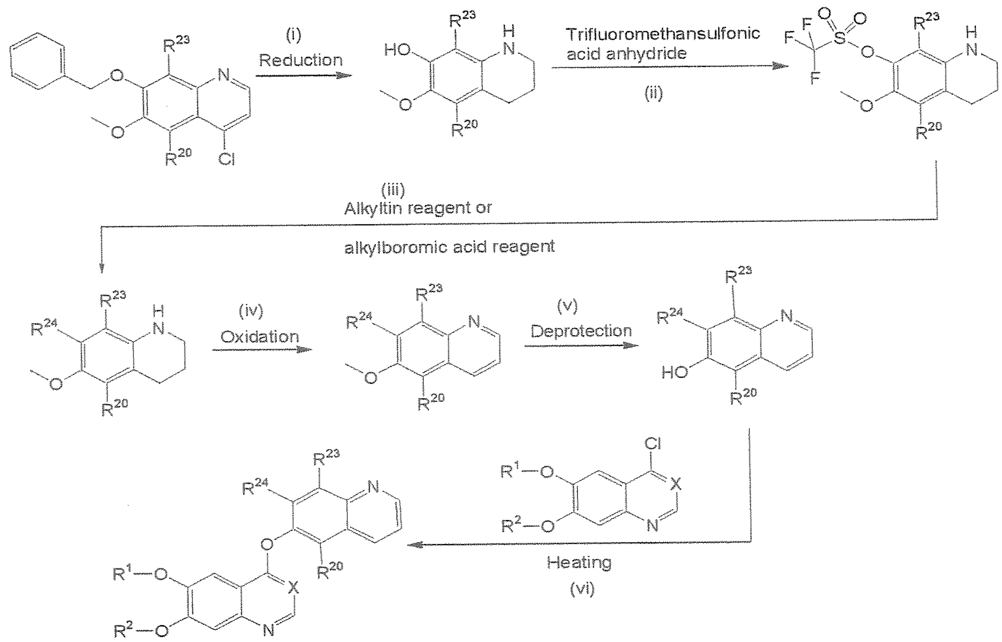


wherein the substituents are as defined above.

[0473] The aimed compounds can be produced by reacting a 6-benzyloxy-4-chloroquinoline derivative with a suitable reducing agent, for example, a hydrogen gas/palladium hydroxide) (step (i)), reacting the 6-hydroxyquinoline derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (ii)).

[0474] Scheme r27:

[Chemical formula 65]

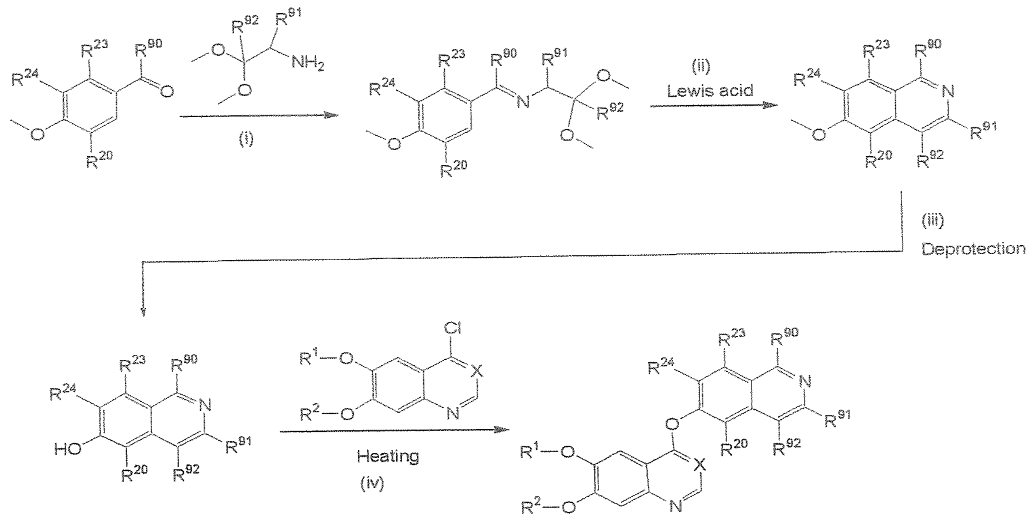


wherein the substituents are as defined above.

[0475] The aimed compounds are produced by reacting a 7-benzyloxy-4-chloroquinoline derivative with a suitable reducing agent, for example, a hydrogen gas/palladium hydroxide (step (i)), then reacting the resultant alcohol with trifluoromethanesulfonic acid anhydride (step (ii)) to give a trifluoromethanesulfonate derivative, reacting the trifluoromethanesulfonate derivative with an alkyltin reagent, for example, tri-n-butyl-(2-pyridyl)-tin, or an alkylboronic acid reagent, for example, 3-pyridylboronic acid in the presence of a suitable transition metal catalyst, for example, tetrakistriphenylphosphine palladium (step (iii)), and reacting the resultant compound with a suitable oxidizing agent, for example, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (step (iv)) to give a quinoline derivative, then reacting the quinoline derivative thus obtained with a suitable reagent, for example, boron tribromide (step (v)) to give 6-hydroxyquinoline derivative, reacting the 6-hydroxyquinoline derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (vi)).

[0476] Scheme r28:

[Chemical formula 66]

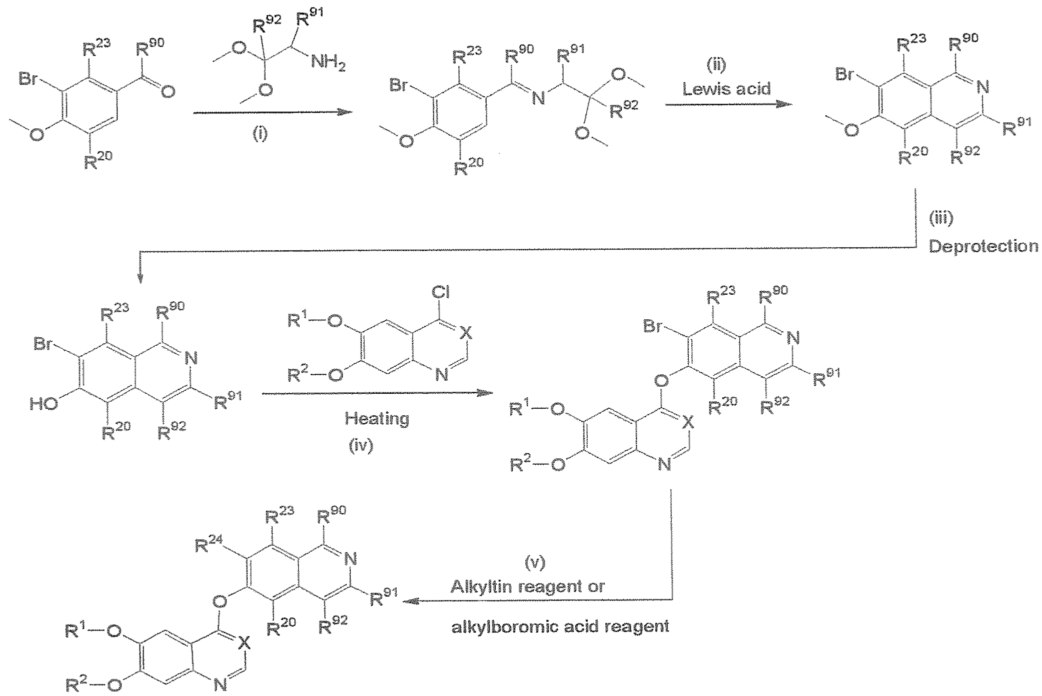


wherein R^{90} to R^{92}, which may be the same or different, represent a hydrogen atom, a halogen atom, C1-2 alkylcarbonyl, C1-2 alkoxycarbonyl, or C1-4 alkyl, and the other substituents are as defined above.

[0477] The aimed compounds can be produced by reacting a 4-methoxybenzaldehyde derivative with a dimethoxyalkylamine derivative (step (i)), reacting the resultant imine derivative with a suitable Lewis acid, for example, titanium tetrachloride (step (ii)) to give a 6-methoxyisoquinoline derivative, reacting the 6-methoxyisoquinoline derivative with a suitable reagent, for example, boron tribromide (step (iii)) to give a 6-hydroxyisoquinoline derivative, then reacting the 6-hydroxyquinoline derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (iv)).

[0478] Scheme r29:

[Chemical formula 67]

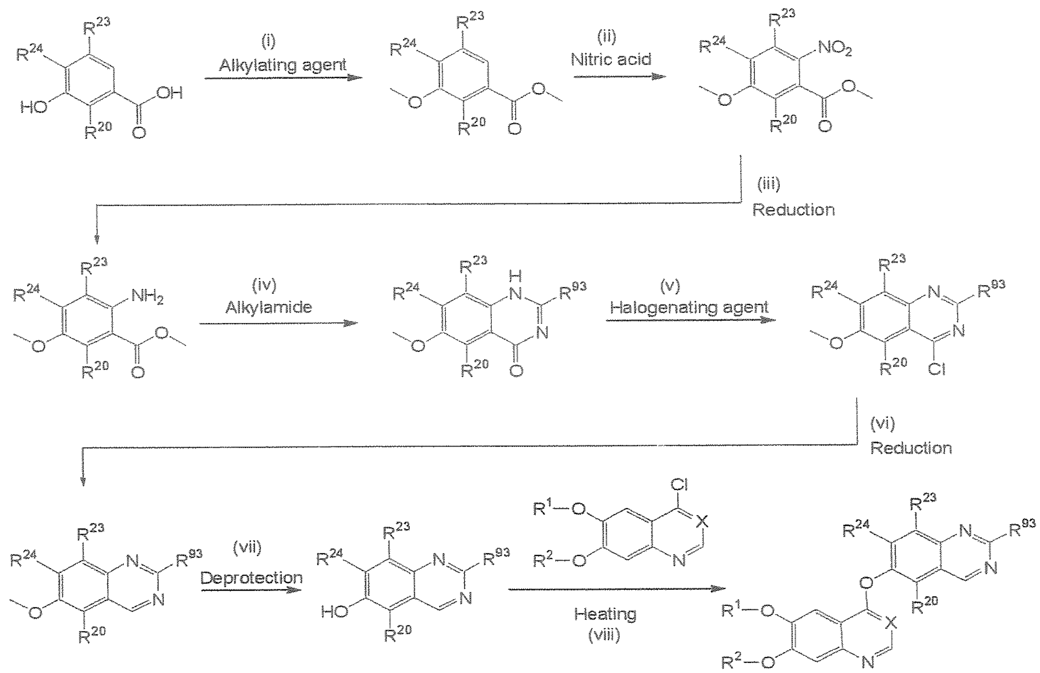


wherein the substituents are as defined above.

The aimed compounds can be produced by reacting a 3-bromo-4-methoxybenzaldehyde derivative with a dimethoxyalkylamine derivative (step (i)), then reacting the resultant imine derivative with a suitable Lewis acid, for example, titanium tetrachloride (step (ii)) to give a 6-methoxyisoquinoline derivative, reacting the 6-methoxyisoquinoline derivative with a suitable reagent, for example, boron tribromide (step (iii)) to give a 6-hydroxyisoquinoline derivative, then reacting the 6-hydroxyquinoline derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (iv)) and reacting the resultant compound with an alkyltin reagent, for example, tri-n-butyl-(2-pyridyl)-tin, or an alkylboronic acid reagent, for example, 3-pyridylboronic acid, in the presence of a suitable transition metal catalyst, for example, tetrakistriphenylphosphine palladium) (step (v)).

[0479] Scheme r30:

[Chemical formula 68]



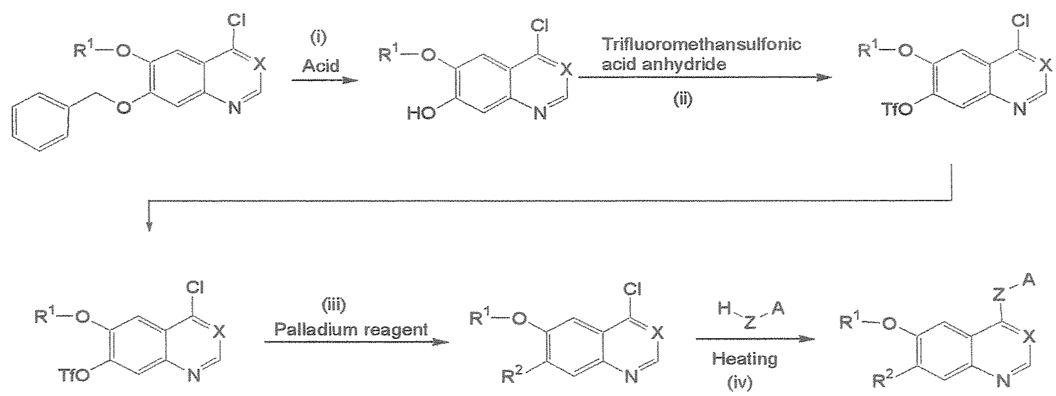
wherein R^{93} represents a hydrogen atom, a halogen atom, C1-2 alkylcarbonyl, C1-2 alkoxycarbonyl, or C1-4 alkyl, and the other substituents are as defined above.

[0480] The aimed compounds can be produced by reacting a 3-hydroxybenzoic acid derivative with an alkylating agent, for example, methyl iodide (step (i)) to give an alkyl 3-alkoxybenzoate derivative, reacting the alkyl 3-alkoxybenzoate derivative with nitric acid in the presence of a suitable acid, for example, acetic acid (step (ii)), then reducing the resultant nitro group with a suitable reducing agent, for example, a hydrogen gas/palladium hydroxide (step (iii)) to give an aniline derivative, reacting the amino group in the aniline derivative with an alkyl amide (step (iv)), then reacting the resultant compound with a suitable halogenating agent, for example, phosphorus oxychloride (step (v)) to give a 4-chloroquinazoline derivative, then reducing the 4-chloroquinazoline derivative with a suitable reducing agent, for example, a hydrogen gas/palladium hydroxide (step (vi)),

then reacting the resultant compound with a suitable reagent, for example, boron tribromide (step (vii)) to give a 6-hydroxyquinazoline derivative, and reacting the 6-hydroxyquinazoline derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (viii)).

[0481] Scheme r31:

[Chemical formula 69]

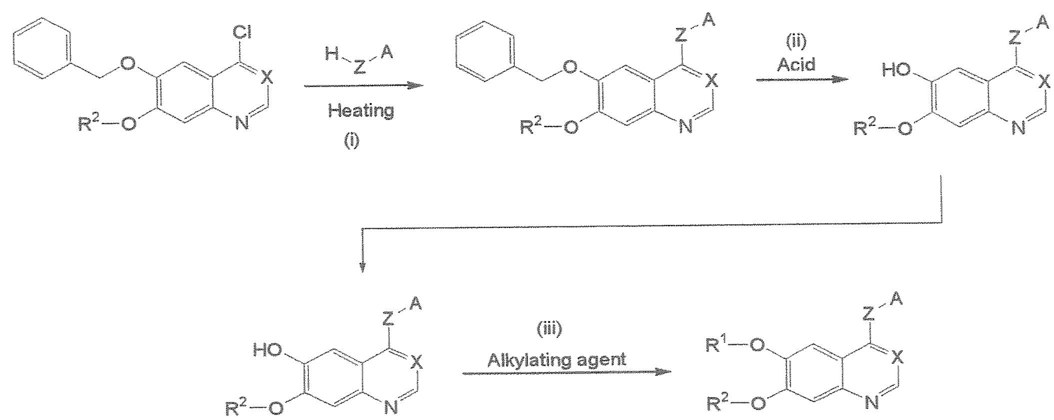


wherein the substituents are as defined above.

[0482] The aimed compounds can be produced by reacting a 7-benzyloxy-4-chloroquinoline derivative or a corresponding quinazolone derivative with a suitable acid, for example, methanesulfonic acid/trifluoroacetic acid (step (i)), then reacting the resultant alcohol with trifluoromethanesulfonic acid anhydride (step (ii)) to give a trifluoromethanesulfonate derivative, reacting the trifluoromethanesulfonate derivative with an amine or an alkene in the presence of a suitable transition metal catalyst, for example, tetrakistriphenylphosphine palladium (step (iii)), and reacting the resultant compound with a phenol derivative or a corresponding aniline derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (iv)).

[0483] Scheme r32:

[Chemical formula 70]

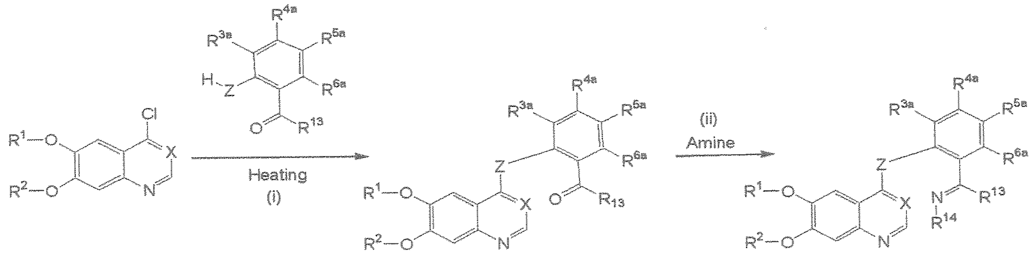


wherein the substituents are as defined above.

The aimed compounds can be produced by reacting a 6-benzyloxy-4-chloroquinoline derivative or a corresponding quinazolone derivative with a phenol derivative or a corresponding aniline derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (i)), then reacting the resultant compound with a suitable acid, for example, methanesulfonic acid/trifluoroacetic acid (step (ii)) to give 6-hydroxyquinoline derivative, and reacting the 6-hydroxyquinoline derivative with an alkylating agent, for example, 1-bromo-2-chloroethane (step (iii)).

[0484] Scheme r33:

[Chemical formula 71]



wherein R^{3a} to R^{6a}, which may be the same or different, represent a hydrogen atom, a halogen atom, or C1-6 alkyl,

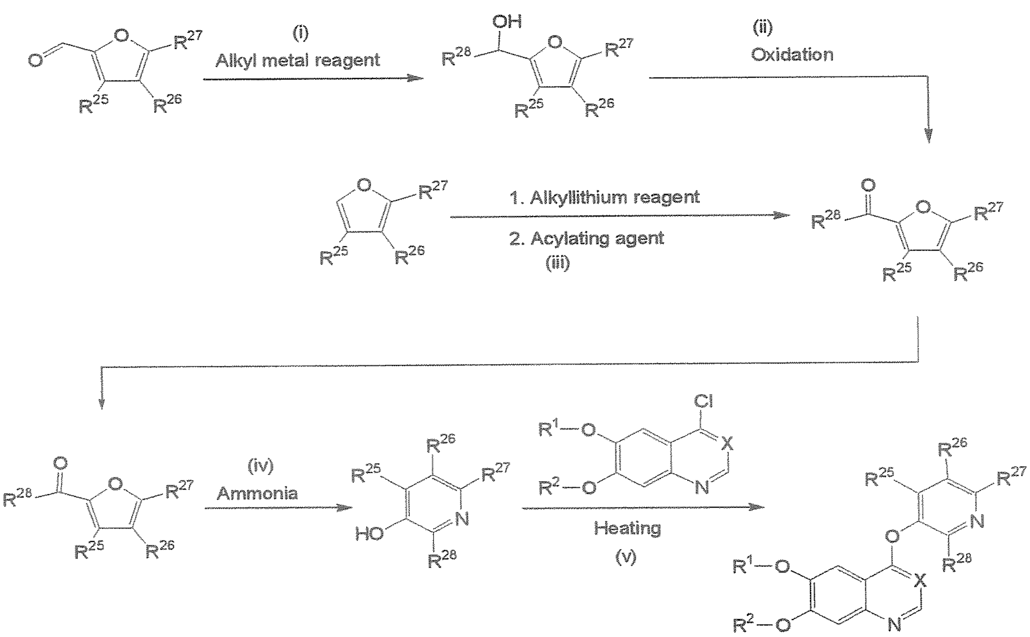
and

the other substituents are as defined above.

[0485] The aimed compounds can be produced by reacting a 4-chloroquinoline derivative or a corresponding quinazolone derivative with a phenol derivative or a corresponding aniline derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (i)) and then reacting the resultant compound with an amine derivative (step (ii)).

[0486] Scheme r34:

[Chemical formula 72]



wherein the substituents are as defined above.

[0487] In this scheme, the aimed compounds can be synthesized through the following two routes.

(I) The aimed compounds can be produced by reacting a furfural derivative with an alkyl metal reagent, for example, phenylmagnesium bromide (step (i)) to give an alcohol derivative, oxidizing the alcohol derivative with a suitable oxidizing agent, for example, manganese dioxide (step (ii)) to give a ketone derivative, then reacting the ketone

derivative with ammonia (step (iv)) to give a 3-hydroxypyridine derivative, reacting the 3-hydroxypyridine derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (v)).

[0488] (II) The aimed compounds can be produced by reacting a furan derivative with an alkyllithium reagent, for example, n-butyllithium, then reacting the resultant compound with an acylating agent, for example, benzoyl chloride (step (iii)) to give a ketone derivative, reacting the ketone derivative with ammonia (step (iv)) to give a 3-hydroxypyridine derivative, then reacting the 3-hydroxypyridine derivative with a 4-chloroquinoline derivative or a corresponding quinazolone derivative in a suitable solvent, for example, o-dichlorobenzene, or in the absence of a solvent, for example, at 120 to 180°C (step (v)).

[0489] Compound r1 to r469

Compounds r1 to r469 as Reference Examples can be produced according to schemes r1 to r34 as described above. These compounds can also be produced with reference to WO 2004/018430. For typical examples of these compounds, the names of the compounds and the measured data on the actually produced compounds will be summarized below.

[0490] Compound r1: 4-(2-Benzylphenoxy)-6,7-dimethoxyquinoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.90 (s, 2H), 3.96 (s, 3H), 4.05 (s, 3H), 6.31 (d, J = 5.4 Hz, 1H), 7.07 - 7.37 (m, 9H), 7.40 (s, 1H), 7.44 (s, 1H), 8.42 (d, J = 5.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 372 $(M+1)^+$

[0491] Compound r6: 6,7-Dimethoxy-4-[4-methyl-2-(piperidinomethyl)phenoxy]quinoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.25-1.49 (m, 6H), 2.30-2.38 (m, 4H), 2.40 (s, 3H), 3.39 (s, 2H), 4.06 (s, 6H), 6.30 (d, J = 5.4 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 7.14 (dd, J = 1.7 Hz, 8.0 Hz, 1H), 7.39 (d, J = 1.4 Hz, 1H), 7.44 (s, 1H), 7.61 (s, 1H), 8.44 (d, J = 5.4 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 393 $(M+1)^+$

[0492] Compound r7: 6,7-Dimethoxy-4-{4-methoxy-2-[(E)-2-phenyl-1-ethenyl]phenoxy}quinoline
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.85 (s, 3H), 4.00 (s, 3H), 4.01 (s, 3H), 6.29 (d, J = 5.4 Hz, 1H), 6.84 (dd, J = 3.2 Hz, 9.0 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.11 - 7.28 (m, 7H), 7.43 (s, 1H), 7.61 (s, 1H), 8.38 (d, J = 5.4 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 414 $(M+1)^+$

[0493] Compound r9: 1-{2-[(6,7-Dimethoxy-4-quinolyl)oxy]-5-methylphenyl}-1-propanol
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.92 (t, J = 7.3 Hz, 3H), 1.80 (m, 2H), 2.42 (s, 3H), 3.99 (s, 3H), 4.02 (s, 3H), 4.75 (t, J = 6.3 Hz, 1H), 6.24 (d, J = 5.4 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 7.14 (dd, J = 2.2 Hz, 8.0 Hz, 1H), 7.32 (s, 1H), 7.53 (s, 1H), 7.54 (d, J = 1.9 Hz, 1H), 8.13 (d, J = 5.4 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 354 $(M+1)^+$

[0494] Compound r14: N-[2-[(6,7-Dimethoxy-4-quinolyl)oxy]-5-methylphenyl]-N-phenylamine
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.35 (s, 3H), 4.03 (s, 3H), 4.04 (s, 3H), 5.77 (s, 1H), 6.51 (d, J = 5.4 Hz, 1H), 6,76 (m, 1H), 6.96 (m, 1H), 7.01 (d, J = 8.1 Hz, 1H), 7.05 (m, 2H), 7.23 - 7.27 (m, 3H), 7.43 (s, 1H), 7.54 (s, 1H), 8.46 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 387 $(M+1)^+$

[0495] Compound r20:

6,7-Dimethoxy-4-[(1-methyl-5-indolyl)oxy]quinoline

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 3.86 (s, 3H), 4.06 (s, 3H), 4.08 (s, 3H), 6.39 (d, J = 5.5 Hz, 1H), 6.50 (d, J = 3.1 Hz, 1H), 7.06 (dd, J = 2.4 Hz, 8.6 Hz, 1H), 7.15 (d, J = 3.1 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.43 (s, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.6,7 (s, 1H), 8.43 (d, J = 5.5 Hz, 1H)

Mass spectrometric value (FD-MS, m/z): 334 (M^+)

[0496] Compound r23: 6-[(6,7-Dimethoxy-4-quinolyl)oxy]-1,4-dihydro-2H-3,1-benzoxazin-2-one

^{1}H-NMR ($CDCl_3$, 500 MHz): δ 4.06 (s, 3H), 4.09 (s, 3H), 5.36 (s, 2H), 6.47 (d, J = 5.1 Hz, 1H), 7.00 (s, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 7.53 (s, 1H), 8.53 (m, 1H), 9.13 (s, 1H)

Mass spectrometric value (FD-MS, m/z): 352 (M^+)

[0497] Compound r76: {2-[(6,7-Dimethoxy-4-quinolyl)oxy]-4,5-dimethylphenyl}(phenyl)methanone hydrochloride

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 2.43 (s, 3H), 3.93 (s, 3H), 4.12 (s, 3H), 6.65 (d, J = 6.6 Hz, 1H), 7.11 (s, 1H), 7.13 (s, 1H), 7.36 (dd, J = 7.6 Hz, 7.6 Hz, 2H), 7.49 (s, 1H), 7.51 (dd, J = 7.3 Hz, 7.3 Hz, 1H), 7.66 (d, J = 7.1 Hz, 2H), 8.06 (s, 1H), 8.42 (dd, J = 6.6 Hz, 6.6 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 414 $(M\text{-}HCl+1)^+$

[0498] Compound r79: Methyl 3-[(6,7-Dimethoxy-4-quinolyl)oxy]naphthalene-2-carboxylate

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.57 (s, 3H), 4.01 (s, 6H), 6.28 (d, J = 5.4 Hz, 1H), 7.46 - 7.61 (m, 5H), 7.77 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 5.4 Hz, 1H), 8.59 (s, 1H)

Mass spectrometric value (ESI-MS, m/z): 390 $(M+1)^+$

[0499] Compound r115: 4-[(6-Methyl-3-pyridyl)oxy]-6,7-dimethoxyquinoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.63 (s, 3H), 4.06 (s, 3H), 4.06 (s, 3H), 6.44 (d, J = 5.4 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.42 (dd, J = 2.7 Hz, 8.6 Hz, 1H), 7.44 (s, 1H), 7.54 (s, 1H), 8.46 (d, J = 2.7 Hz, 1H), 8.51 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 297 $(M+1)^+$

[0500] <u>Compound r117: 1-{[3-(6,7-Dimethoxy-4-quinolyl)oxy]-6-methyl-2-pyridyl}-1-ethanone</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.63 (s, 3H), 2.67 (s, 3H), 4.05 (s, 3H), 4.05 (s, 3H), 6.28 (d, J = 5.1 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.44 (s, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.57 (s, 1H), 8.47 (d, J = 5.2 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 339 $(M+1)^+$

[0501] <u>Compound r118: 4-(2-Acetyl-4-methoxyphenoxy)-6-methoxy-7-quinolyl 4-morpholine carboxylate</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H), 3.29 (m, 4H), 3.60 (m, 4H), 3.82 (s, 3H), 3.95 (s, 3H), 6.32 (d, J = 5.2 Hz, 1H), 7.02 - 7.09 (m, 2H), 7.36 (d, J = 2.8 Hz, 1H), 7.54 (s, 1H), 7.87 (s, 1H), 8.43 (d, J = 5.2 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 453 $(M+1)^+$

[0502] <u>Compound r163: Ethyl 2-[(6,7-dimethoxy-4-quinolyl)carbonyl]benzoate</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, J = 7.1 Hz, 3H), 3.98 (q, J = 7.1 Hz, 2H), 4.07 (s, 3H), 4.07 (s, 3H), 7.07 (d, J = 4.6 Hz, 1H), 7.51 (s, 1H), 7.53 (dd, J = 1.4 Hz, 7.3 Hz, 1H), 7.64 (m, 1H), 7.66 (m, 1H), 8.02 (m, 1H), 8.33 (s, 1H), 8.69 (d, J = 4.6 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 366 $(M+1)^+$

[0503] <u>Compound r164: 4-(2-Iodo-4,5-dimethyl-phenoxy)-6,7-dimethoxy-quinoline</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.25 (s, 3H), 2.28 (s, 3H), 4.05 (s, 3H), 4.07 (s, 3H), 6.32 (d, J = 5.4 Hz, 1H), 6.97 (s, 1H), 7.44

(s, 1H), 7.61 (s, 1H), 7.68 (s, 1H), 8.48 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 436 $(M+1)^+$

[0504] Compound r175: 1-[5-Benzyloxy-2-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-ethanone
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 3.97 (s, 6H), 5.06 (s, 2H), 6.31 (d, J = 5.2 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 7.13 (dd, J = 8.8 Hz, J = 3.2 Hz, 1H), 7.25 - 7.41 (m, 6H), 7.45 (d, J = 3.2 Hz, 1H), 7.49 (s, 1H), 8.41 (d, J = 5.2 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 430 $(M+1)^+$

[0505] Compound r178: 1-[2-(6,7-Dimethoxy-quinolin-4-yloxy)-5-ethoxy-phenyl]-ethanone
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.38 (t, J = 6.8 Hz, 3H), 2.41 (s, 3H), 3.98 (s, 6H), 4.04 (q, J = 6.8 Hz, 2H), 6.30 (d, J = 5.2 Hz, 1H), 7.00 - 7.07 (m, 2H), 7.34 (d, J = 2.8 Hz, 1H), 7.36 (s, 1H), 7.49 (s, 1H), 8.41 (d, J = 5.2 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 368 $(M+1)^+$

[0506] Compound r193: {1-[2-(6,7-Dimethoxy-quinolin-4-yloxy)-4,5-dimethylphenyl]-ethylidene}-hydrazine
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.96 (s, 3H), 2.27 (s, 3H), 2.31 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 5.17 (brs, 2H), 6.38 (d, J = 5.4 Hz, 1H), 6.91 (s, 1H), 7.37 (s, 1H), 7.45 (s, 1H), 7.56 (s, 1H), 8.44 (d, J = 5.4 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 388 $(M+Na)^+$

[0507] Compound r200: 1-[3-(6,7-Dimethoxy-quinolin-4-yloxy)-naphthalene-2-yl]-ethanone
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.60 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.46 (d, J = 5.2 Hz, 1H), 7.46 (s, 1H), 7.51 - 7.62 (m, 4H), 7.77 (d, J = 8 Hz, 1H), 7.99 (d, 7.6 Hz, 1H), 8.44 (s, 1H), 8.49

(d, J = 5.6 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 374 $(M+1)^+$

[0508] <u>Compound r204: 4-(2-Cyclopentyloxy-pyridin-3-yloxy)-6,7-dimethoxy-quinoline</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 1.23 - 1.81 (m, 8H), 4.06 (s, 3H), 4.06 (s, 3H), 5.43 (m, 1H), 6.31 (d, J = 5.1 Hz, 1H), 6.95 (dd, J = 1.1, 7.6 Hz, 1H), 7.43 (s, 1H), 7.49 (m, 1H), 7.58 (s, 1H), 8.10 (m, 1H), 8.46 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 367 $(M+1)^+$

[0509] <u>Compound r207: 6,7-Dimethoxy-4-(6-methoxy-pyridin-3-yloxy)-quinoline</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.89 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 6.31 (d, J = 5.2 Hz, 1H), 6.76 (d, J = 9.2 Hz, 1H), 7.31 - 7.39 (m, 2H), 7.47 (s, 1H), 8.02 (d, J = 2.8 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 313 $(M+1)^+$

[0510] <u>Compound r211: 4-(6-Fluoro-2-iodo-pyridin-3-yloxy)-6,7-dimethoxy-quinoline</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.99 (s, 3H), 4.00 (s, 3H), 6.27 (d, J = 5.6 Hz, 1H), 6.95 (dd, J = 8.4 Hz, 3.6 Hz, 1H), 7.37 - 7.50 (m, 3H), 8.47 (d, J = 5.2 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 875 $(2M+Na)^+$

[0511] <u>Compound r213: 3-(6,7-Dimethoxy-quinolin-4-yloxy)-6-methyl-pyridin-2-carbonitrile</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.65 (s, 3H), 4.05 (s, 3H), 4.06 (s, 3H), 6.54 (d, J = 5.1 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.46 (s, 1H), 7.46 (s, 1H), 8.59 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 344 $(M+Na)^+$

[0512] <u>Compound r223:</u>

6,7-Dimethoxy-4-(6-methyl-2-phenyl-pyridin-3-yloxy)-quinoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.69 (s, 3H), 4.03 (s, 3H), 4.05 (s, 3H), 6.39 (d, J = 5.4 Hz, 1H), 7.22 - 7.59 (m, 5H), 7.65 - 7.70 (m, 2H), 7.81 - 7.84 (m, 2H), 8.42 (dd, J = 2.0, 5.6 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 373 $(M+1)^+$

[0513] Compound r256: 4-[2-(1,5-Dimethyl-1H-pyrazol-3-yl)-6-methyl-pyridin-3-yloxy]-6,7-dimethoxy-quinoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.13 (s, 3H), 2.71 (s, 3H), 3.75 (s, 3H), 4.06 (s, 3H), 4.07 (s, 3H), 6.33 (d, J = 5.4 Hz, 1H), 6.41 (s, 1H), 7.17 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.65 (s, 1H), 8.42 (d, J = 5.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 413 $(M+Na)^+$

[0514] Compound r260: 4-[2-(4,5-Dimethylthiazol-2-yl)-5,6-dimethyl-pyridin-3-yloxy]-6,7-dimethoxy-quinoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.13 (s, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 2.64 (s, 3H), 4.07 (s, 3H), 4.07 (s, 3H), 6.33 (d, J = 5.1 Hz, 1H), 7.33 (s, 1H), 7.45 (s, 1H), 7.71 (s, 1H), 8.42 (d, J = 5.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 444 $(M+Na)^+$

[0515] Compound r277: [3-(6,7-Dimethoxy-quinolin-4-yloxy)-quinolin-2-ylmethyl]-diisopropyl-amine

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 0.91 - 0.95 (m, 12H), 3.06 (m, 2H), 4.05 (s, 3H), 4.06 (s, 3H), 4.10 (s, 2H), 6.48 (d, J = 5.4 Hz, 1H), 7.46 (s, 1H), 7.54 (m, 1H), 7.61 (s, 1H), 7.70 - 7.73 (m, 2H), 7.73 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H), 8.51 (d, J = 5.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 446 $(M+1)^+$

[0516] Compound r278: 1-[3-(6,7-Dimethoxy-quinolin-4-yloxy)-quinolin-2-yl]-ethanone

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.70 (s, 3H), 3.99 (s, 6H), 6.30 (d, J = 5.2 Hz, 1H), 7.42 (s, 1H), 7.53 - 7.66 (m, 2H), 7.76 (m, 2H), 7.90 (s, 1H), 8.16 (d, J = 9.2 Hz, 1H), 8.41 (d, J = 5.2 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 375 $(M+1)^+$

[0517] <u>Compound r281: 4-(2-Bromo-quinolin-3-yloxy)-6,7-dimethoxy-quinoline</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.05 (s, 6H), 6.44 (d, J = 5.2 Hz, 1H), 7.50 (s, 1H), 7.54 - 7.65 (m, 2H), 7.70 - 7.79 (m, 2H), 7.89 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.51 (d, J = 5.2 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 411 $(M+1)^+$

[0518] <u>Compound r283: 6,7-Dimethoxy-4-(2-phenyl-quinolin-3-yloxy)-quinoline</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.02 (s, 3H), 4.05 (s, 3H), 6.47 (d, J = 5.1 Hz, 1H), 7.32 - 7.36 (m, 3H), 7.41 (s, 1H), 7.50 (s, 1H), 7.59 (m, 1H), 7.76 (m, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.95 - 7.98 (m, 3H), 8.24 (d, J = 8.6 Hz, 1H), 8.45 (d, J = 5.1 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 409 $(M+1)^+$

[0519] <u>Compound r284: {3-[3-(6,7-Dimethoxy-quinolin-4-yloxy)-quinolin-2-yl]-phenyl}-methanol</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.86 (s, 3H), 3.95 (s, 3H), 4.56 (s, 2H), 6.24 (d, J = 5.2 Hz, 1H), 7.16 - 7.24 (m, 3H), 7.42 (s, 1H), 7.49 (m, 1H), 7.68 (m, 2H), 7.80 (d, J = 5.2 Hz, 1H), 7.84 (s, 1H), 8.01 (s, 1H), 8.12 (m, 2H)
Mass spectrometric value (ESI-MS, m/z): 437 $(M-1)^-$

[0520] <u>Compound r297: 6,7-Dimethoxy-4-(7-methoxy-quinolin-6-yloxy)-quinoline</u>
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.93 (s, 3H), 4.06 (s, 3H), 4.07 (s, 3H), 6.38 (d, J = 5.1 Hz, 1H), 7.34 (dd, J = 4.4, 8.3 Hz, 1H), 7.45 (s, 1H), 7.56 (s, 1H), 7.63 (s, 1H), 7.63 (s, 1H), 8.05 (d, J = 8.1 Hz, 1H), 8.48 (d, J = 5.1 Hz, 1H), 8.88 (dd, J = 1.4, 4.4

Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 363 $(M+1)^+$

[0521] Compound r299: 6,7-Dimethoxy-4-(7-phenyl-quinolin-6-yloxy)-quinoline
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.01 (s, 3H), 4.03 (s, 3H), 6.47 (d, J = 5.4 Hz, 1H), 7.23 - 7.32 (m, 3H), 7.38 (s, 1H), 7.44 - 7.47 (m, 2H), 7.61 - 7.63 (m, 3H), 8.12 (d, J = 7.8 Hz, 1H), 8.30 (s, 1H), 8.43 (d, J = 5.1 Hz, 1H), 8.97 (dd, J = 1.7, 4.2 Hz, 1H)
Mass spectrometric value (ESI-MS, m/z): 409 $(M+1)^+$

[0522] Compound r300: 6,7-Dimethoxy-4-(7-methyl-isoquinolin-6-yloxy)-quinoline
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 6.35 (d, J = 5.2 Hz, 1H), 7.36 (s, 1H), 7.39 (s, 1H), 7.47 (m, 2H), 7.86 (s, 1H), 8.41 (d, J = 5.6 Hz, 1H), 8.44 (d, J = 5.2 Hz, 1H), 9.15 (s, 1H)
Mass spectrometric value (ESI-MS, m/z): 347 $(M+1)^+$

[0523] Compound r301: 4-(7-Bromo-isoquinolin-6-yloxy)-6,7-dimethoxy-quinoline
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.97 (s, 3H), 3.99 (s, 3H), 6.44 (d, J = 5.2 Hz, 1H), 7.40 (s, 1H), 7.49 (m, 3H), 8.32 (s, 1H), 8.50 (m, 2H), 9.17 (s, 1H)
Mass spectrometric value (ESI-MS, m/z): 412 $(M+1)^+$

[0524] Compound r303: 6,7-Dimethoxy-4-(7-pyridin-2-yl-isoquinolin-6-yloxy)-quinoline
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.93 (s, 3H), 3.97 (s, 3H), 6.27 (d, J = 5.2 Hz, 1H), 7.12 (m, 1H), 7.34 (s, 1H), 7.41 (s, 1H), 7.51 (m, 3H), 7.71 (d, J = 7.6 Hz, 1H), 8.40 (d, J = 5.2 Hz, 1H), 8.49 (d, J = 6.0 Hz, 1H), 8.52 (s, 1H), 8.60 (d, J = 4.4 Hz, 1H), 9.31 (s, 1H)
Mass spectrometric value (ESI-MS, m/z): 432 $(M+Na)^+$

[0525] Compound r305:

6-(6,7-Dimethoxy-quinolin-4-yloxy)-7-methyl-quinazoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.51 (s, 3H), 4.07 (s, 3H), 4.10 (s, 3H), 6.45 (d, J = 5.4 Hz, 1H), 7.57-7.59 (m, 3H), 8.06 (s, 1H), 8.53 (d, J = 5.4 Hz, 1H), 9.31 (s, 1H), 9.34 (s, 1H)

Mass spectrometric value (ESI-MS, m/z): 348 $(M+1)^+$

[0526] Compound r320: 1-{2-[6-Methoxy-7-(3-morpholin-4-yl-propoxy)-quinolin-4-yloxy]-4,5-dimethyl-phenyl}-ethanone hydrochloride

^{1}H-NMR (CD_3OD, 400 MHz): δ 2.25 - 2.55 (m, 11H), 3.22 (m, 2H), 3.49 (m, 2H), 3.67 (d, J = 12.0 Hz, 2H), 3.86 (t, J = 12.0 Hz, 2H), 4.02 - 4.18 (m, 5H), 4.47 (m, 2H), 6.76 (d, J = 5.2 Hz, 1H), 7.22 (s, 1H), 7.52 (s, 1H), 7.84 (s, 1H), 7.92 (s, 1H), 8.60 (d, J = 5.2 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 465 $(M+1-2HCl)^+$

[0527] Compound r351: 7-Benzyloxy-6-methoxy-4-(2-methyl-quinolin-3-yloxy)-quinoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.66 (s, 3H), 4.07 (s, 3H), 5.35 (s, 2H), 6.37 (d, J = 5.1 Hz, 1H), 7.29 - 7.37 (m, 1H), 7.37 - 7.44 (m, 2H), 7.49 - 7.57 (m, 4H), 7.61 (s, 1H), 7.72 (ddd, J = 1.5, 6.8, 8.3 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.80 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.48 (d, J = 5.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 423 $(M+1)^+$

[0528] Compound r352: 6-Methoxy-4-(2-methyl-quinolin-3-yloxy)-quinolin-7-ol

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 2.54 (s, 3H), 3.93 (s, 3H), 6.43 (d, J = 5.1 Hz, 1H), 7.31 (s, 1H), 7.52 - 7.62 (m, 2H), 7.73 (dd, J = 7.1, 7.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 8.13 (s, 1H), 8.40 (d, J = 5.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 333 $(M+1)^+$

[0529] Compound r383: 6-Methoxy-4-(2-methyl-quinolin-3-yloxy)-7-oxilanyl methoxy-quinoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.66 (s, 3H), 2.83 - 2.89 (m, 1H), 2.94 - 3.01 (m, 1H), 3.49 - 3.57 (m, 1H), 4.06 (s, 3H), 4.21 (dd, J = 5.6, 11.2 Hz, 1H), 4.46 (dd, J = 3.4, 11.5 Hz, 1H), 6.38 (d, J = 5.4 Hz, 1H), 7.48 (s, 1H), 7.55 (dd, J = 7.8, 7.8 Hz, 1H), 7.60 (s, 1H), 7.69 - 7.80 (m, 2H), 7.82 (s, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.50 (d, J = 5.2 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 389 $(M+1)^+$

[0530] Compound r384: 3-[6-Methoxy-4-(2-methyl-quinolin-3-yloxy)-quinolin-7-yloxy]-propane-1,2-diol

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.65 (s, 3H), 3.86 - 3.97 (m, 2H), 4.04 (s, 3H), 4.22-4.35 (m, 2H), 4.39 (dd, J = 3.9, 9.8 Hz, 1H), 6.41 (d, J = 5.4 Hz, 1H), 7.55 (dd, J = 7.6, 7.6 Hz, 1H), 7.57 (s, 1H), 7.60 (s, 1H), 7.72 (d, J = 7.1 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.83 (s, 1H), 8.11 (d, J = 8.6 Hz, 1H), 8.50 (d, J = 5.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 407 $(M+1)^+$

[0531] Compound r410: [6-Methoxy-4-(2-methyl-quinolin-3-yloxy)-quinolin-7-yl]-(2-morpholin-4-yl-ethyl)-amine

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.53 (s, 3H), 2.68 (s, 3H), 2.76 (m, 2H), 3.38 (m, 2H), 3.76 (m, 4H), 4.04 (s, 3H), 5.41 (m, 1H), 6.28 (d, J = 5.4 Hz, 1H), 7.08 (s, 1H), 7.44 (s, 1H), 7.53 (m, 1H), 7.68 - 7.74 (m, 2H), 7.76 (s, 1H), 8.09 (d, J = 8.6 Hz, 1H), 8.42 (d, J = 5.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 445 $(M+1)^+$

[0532] Compound r415: 6-Benzyloxy-7-methoxy-4-(2-methyl-quinolin-3-yloxy)-quinoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.61 (s, 3H), 4.06 (s, 3H), 5.32 (s, 2H), 6.41 (d, J = 5.1 Hz, 1H), 7.22 - 7.40 (m, 3H), 7.44 - 7.58 (m, 4H), 7.61 (s, 1H), 7.67 - 7.76 (m, 3H), 8.09 (d, J = 8.3 Hz, 1H), 8.51 (d, J = 5.1 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 423 $(M+1)^+$

[0533] Compound r416: 6-(2-Imidazol-1-yl-ethoxy)-7-methoxy-4-(2-methyl-quinolin-3-yloxy)-quinoline

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 2.62 (s, 3H), 4.06 (s, 3H), 4.39 - 4.54 (m, 4H), 6.36 (d, J = 5.2 Hz, 1H), 7.08 (s, 1H), 7.15 (s, 1H), 7.48 (s, 1H), 7.50 - 7.59 (m, 2H), 7.68 - 7.78 (m, 3H), 7.79 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.51 (d, J = 5.4 Hz, 1H)

Mass spectrometric value (ESI-MS, m/z): 449 $(M+Na)^+$

[0534] Evaluation test

Test Example 1A: TGFβ signal inhibitory activity (in vitro test)

The compounds according to the present invention was evaluated for TGFβ signal inhibitory activity according to the method described in J. Boil .Chem., 273, 21145-21152 (1998).

Specifically, a plasmid having four tandem binding sequences of Smad3, a TGF-beta signal transducer, to the upstream of a luciferases gene were used as a reporter plasmid ((SBE)4-Luc) to detect TGF-beta signal,

. This reporter gene was introduced into human pulmonary carcinoma epithelial cells (A549) (available from ATCC) to establish a stable cell line.

A test compound and TGFβ-1 (2 ng/ ml) were added to the cells, and the mixture was cultured for 4 hr. In this case, the compounds according to the present invention synthesized in the Examples were used as the test compound. After the culture, the luciferase activity of the cells were measured by chemiluminescence (Steady Glo (trademark) luciferase assay system, available from Promega).

Likewise, the luciferase activity was measured as a control against the culture of cells with the addition of TGFβ only and the culture of cells without the addition of both TGFβ and the test compound.

[0535] The TGFβ inhibition (%) was calculated by the following equation, based on the measurement results.

$$\text{TGF}\beta \text{ inhibition (\%)} = (A - B)/(A - C) \times 100$$

wherein

A: luciferase activity with the addition of TGFβ1 and without the addition of test compound (relative luciferase unit),

B: luciferase activity with the addition of both TGFβ1 and test compound (relative luciferase unit), and

C: luciferase activity without the addition of both TGFβ1 and test compound (relative luciferase unit).

[0536] The test was carried out for each of test compound at the concentrations of 3 μM and 10 μM. For certain test compounds, the test was further carried out for test compound at the concentration of 1 μM.

The results were as shown in Table 1A.

The results show that the compounds according to the present invention have antagonistic activities against the action of TGFβ.

[0537] <u>Test Example 1B: TGFβ signal inhibitory activity (in vitro test)</u>

For the compounds of Reference Examples, the TGFβ signal inhibitory activity was evaluated in the same manner as in Test Example 1A.

The results were as shown in Table 1B

[0538] Table A:

[Table 1]

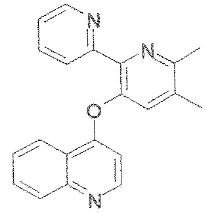
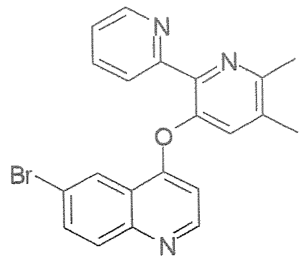
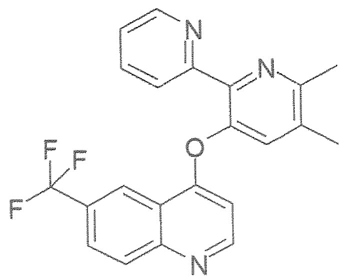
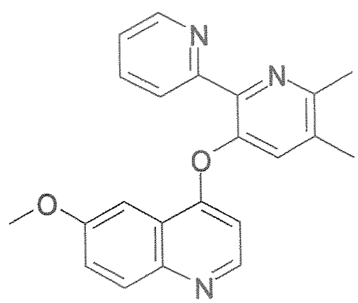
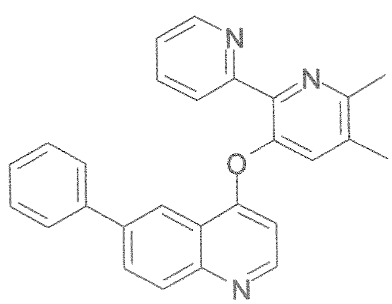
Compound	Name of compound	Measured molecular weight
178	2-[6-Methoxy-4-(2-phenyl-[1,8]naphthyridin-3-yloxy)-quinolin-7-yloxy]-ethanol	462(M+Na)+
179	4-(6-Ethyl-[2,2′]bipyridinyl-3-yloxy)-6-methoxy-quinoline-7-carboxylic acid amide	423(M+Na)+
180	3-(2-Tert-butyl-thieno[3,2-b]pyridin-7-yloxy)-6-ethyl-[2,2′]bipyridine	412(M+Na)+
181	2-[4-(6-Ethyl-[2,2′]bipyridinyl-3-yloxy)-quinolin-6-yloxy]-ethanol	410(M+Na)+
182	2-[4-(6-Ethyl-[2,2′]bipyridinyl-3-yloxy)-quinolin-6-yloxy]-ethyl acetate	452(M+Na)+
183	3-(6-Benzyloxy-quinolin-4-yloxy)-6-ethyl-[2,2′]bipyridine	456(M+Na)+
184	4-(6-Ethyl-[2,2′]bipyridinyl-3-yloxy)-quinolin-6-ol	366(M+Na)+
185	6-Chloro-4-(6-ethyl-[2,2′]bipyridinyl-3-yloxy)-quinoline-7-carboxylic acid amide	427(M+Na)+
186	4-(6-Ethyl-[2,2′]bipyridinyl-3-yloxy)-quinolin-6-yl acetate	408(M+Na)+
187	4-(6-Ethyl-[2,2′]bipyridinyl-3-yloxy)-quinolin-6-yl methanesulfonate	444(M+Na)+
188	6,7-Dimethoxy-4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline	397(M+Na)+
189	1-{2-[4-(6-Ethyl-[2,2′]bipyridinyl-3-yloxy)-quinolin-6-yloxy]-ethyl}-3-propyl-urea	494(M+Na)+
190	6-Benzyloxy-4-(6-ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline	457(M+Na)+
191	4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-ol	343(M-1)-
192	2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethanol	411(M+Na)+
193	6-Benzyloxy-4-(6-ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline-7-carboxylic acid amide	500(M+Na)+
194	4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-6-hydroxy-quinoline-7-carboxylic acid amide	386(M-1)-

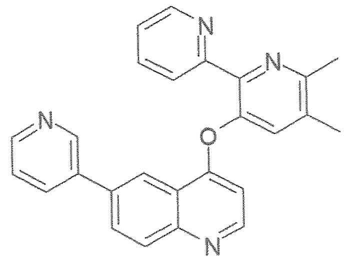
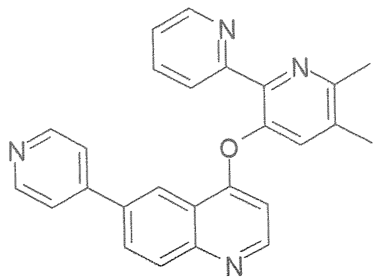
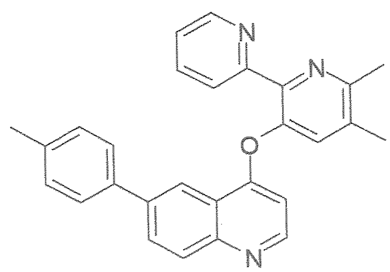
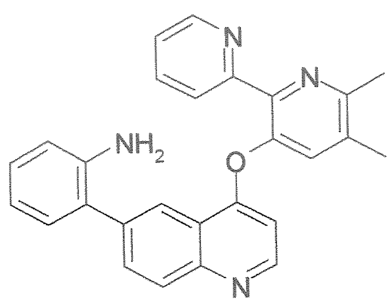
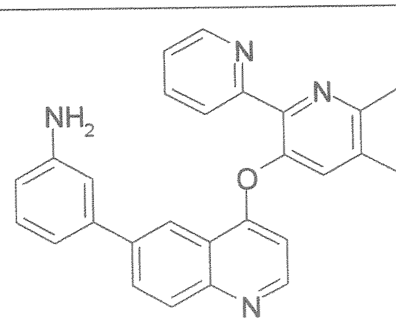
Compound	Name of compound	Measured molecular weight
200	2-[4-(5,6-Dimethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethanol	411(M+Na)+
201	4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-ol	329(M-1)-
202	2-[4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethanol	397(M+Na)+
203	N-{2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethyl}-methanesulfonic acid amide	488(M+Na)+
204	2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethylamine	410(M+Na)+
205	2-[4-(6-Methyl-[2,2']bipyridinyl-3-yloxy)-quinolin-6-yloxy]-ethanol	374(M+1)+
206	2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethyl acetate	453(M+Na)+
207	2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethyl 2,2-dimethyl-propanate	495(M+Na)+
208	2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethyl (S)-2-amino-3-methyl-butanoate	510(M+Na)+
209	4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-6-(2-morpholin-4-yl-ethoxy)-quinoline	466(M+Na)+
210	6-(3-Chloro-propoxy)-4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline	429(M+Na)+
211	2-(Methyl-{3-[4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-propyl}-amino)-ethanol	468(M+Na)+
212	4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-6-(3-piperidin-1-イル-propoxy)-quinoline	478(M+Na)+
213	6-Cyclobutylmethoxy-4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline	421(M+Na)+
214	6-(2,2-Dimethyl-propoxy)-4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline	423(M+Na)+

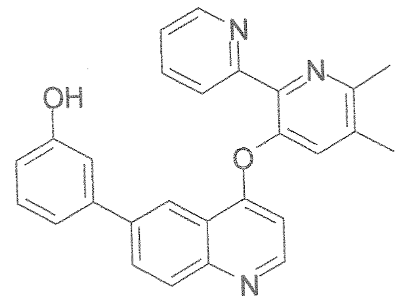
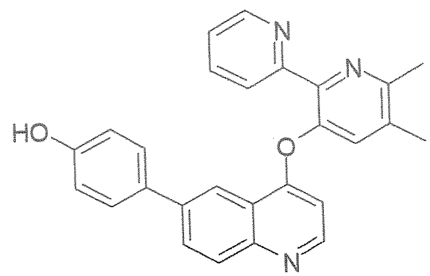
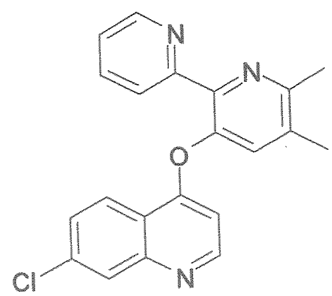
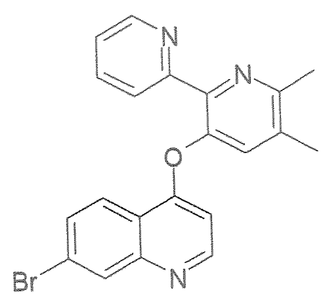
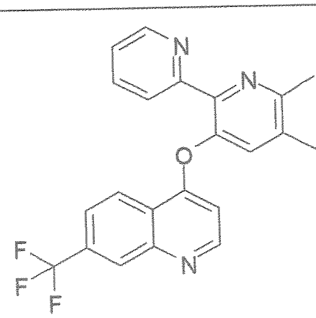
Compound	Name of compound	Measured molecular weight
215	2,2-Dimethyl-3-[4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-propan-1-ol	439(M+Na)+
216	6-(2-Cyclohexylethoxy)-4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline	463(M+Na)+
217	4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline-7-carboxylic acid amide	380(M+Na)+
218	4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-6-[3-(4-pyridin-2-yl- piperazin-1-yl)-propoxy]-quinoline	556(M+Na)+
219	2-({3-[4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-propyl}-phenylamino)-ethanol	530(M+Na)+
220	6-[3-(4-Benzyl-piperidin-1-yl)-propoxy]-4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinoline	568(M+Na)+
221	2-(4-{3-[4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-propyl}-piperazin-1-yl)-ethanol	523(M+Na)+
222	3-[4-(6-Methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-propan-1-ol	411(M+Na)+
223	ethyl-methyl-{2-[4-(6-methyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethyl}-amine	438(M+Na)+
224	2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-quinolin-6-yloxy]-ethyl 2,2-dimethyl-butanoate	509(M+Na)+
225	2-[4-(6-Ethyl-2-pyrimidin-2-yl-pyridin-3-yloxy)-7-fluoro-quinolin-6-yloxy]-ethanol	429(M+Na)+

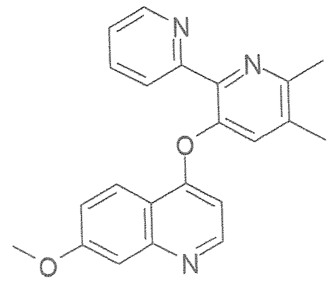
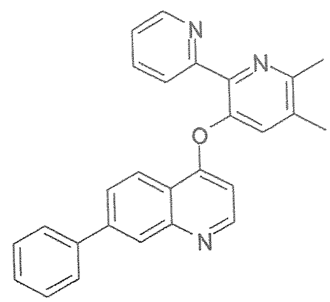
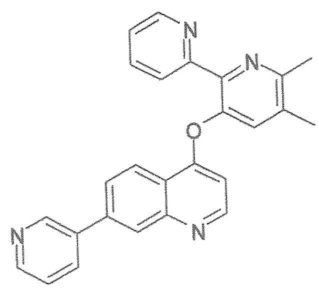
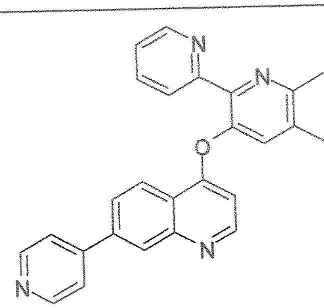
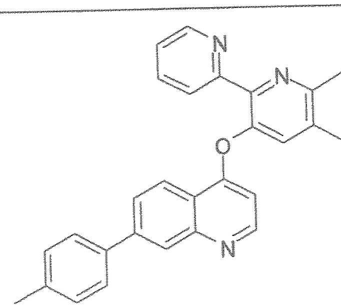
[0539] Table 1A:

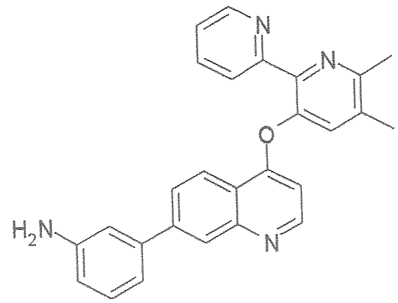
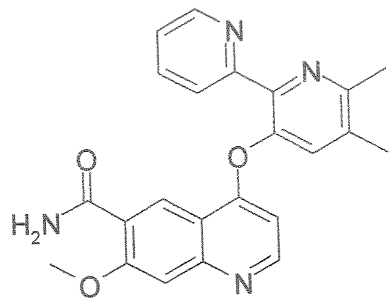
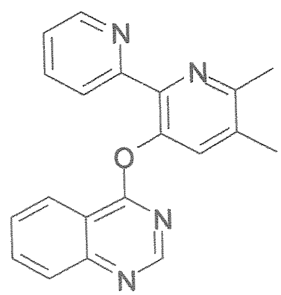
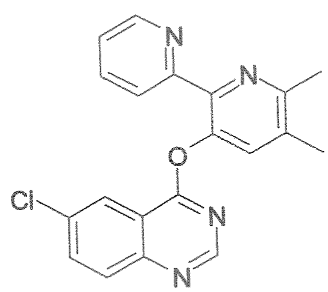
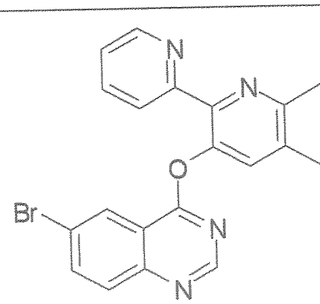
[Table 1A]

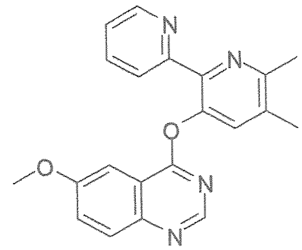
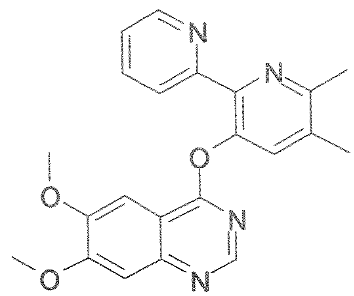
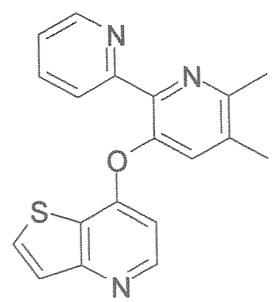
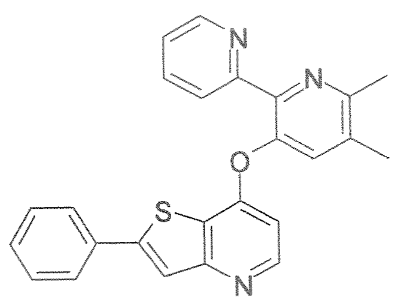
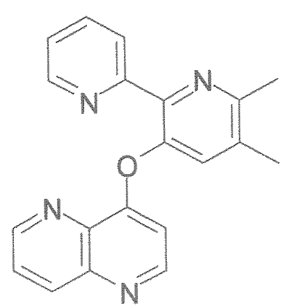
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
1		100	100	
2		100	100	
3			99	79
4			100	94
5		100	79	

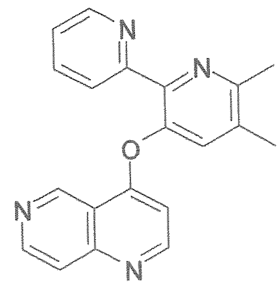
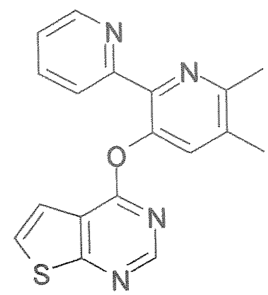
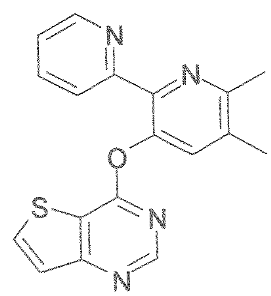
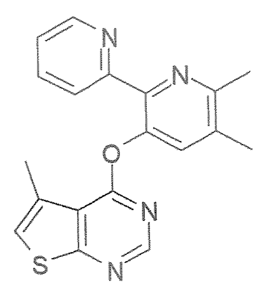
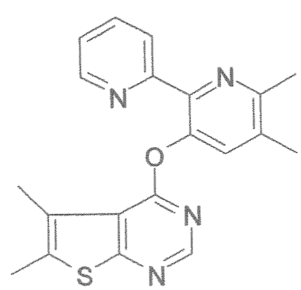
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
6		100	100	
7		100	100	
8		100	60	
9		100	87	
10		100	100	

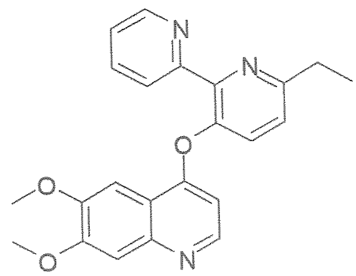
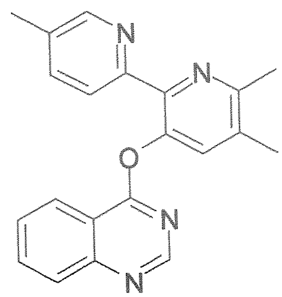
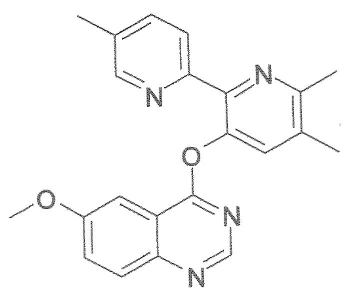
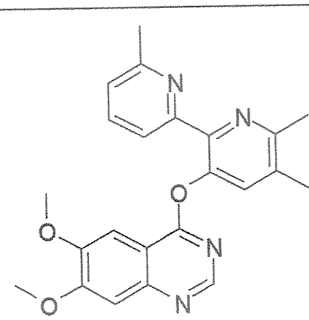
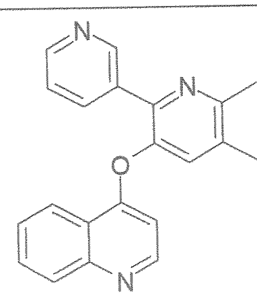
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
11		100	100	
12		100	100	
13		100	99	
14		100	100	
15		100	99	

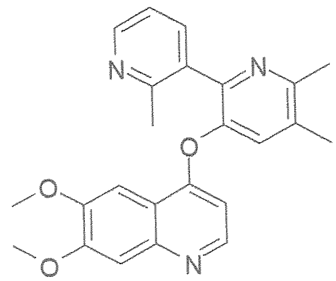
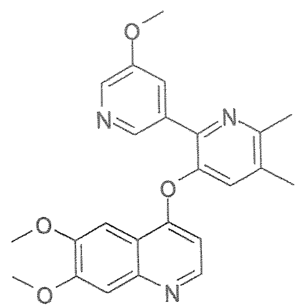
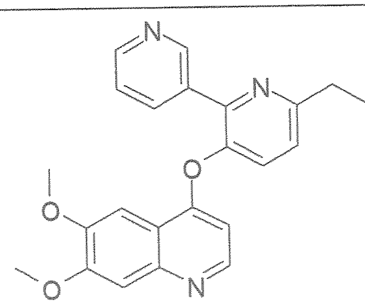
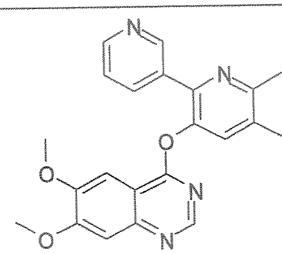
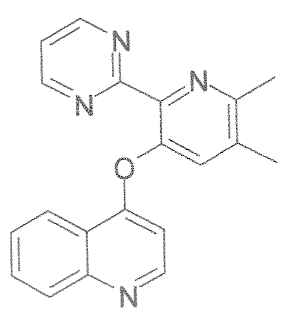
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
16			100	97
17		100	98	
18		100	95	
19		100	100	
20		100	90	

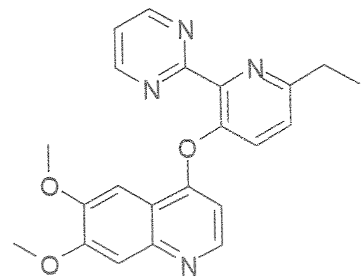
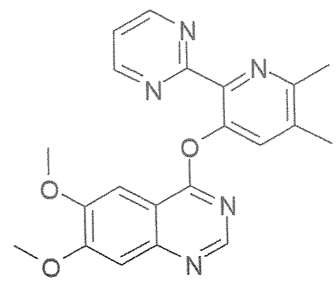
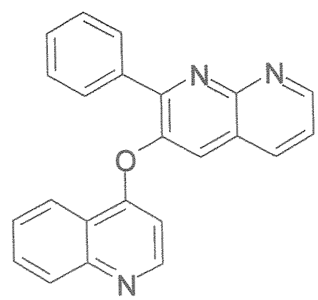
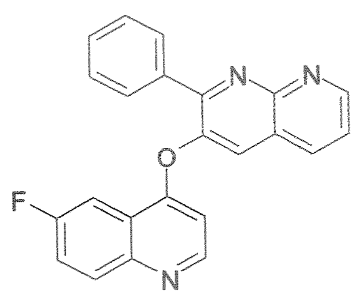
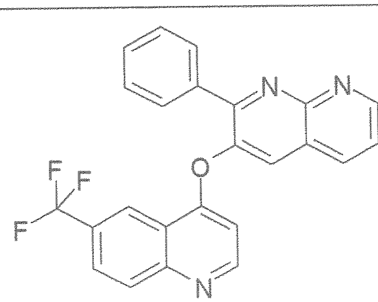
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
21		100	99	
22			99	81
23		98	78	
24		99	90	
25		99	89	

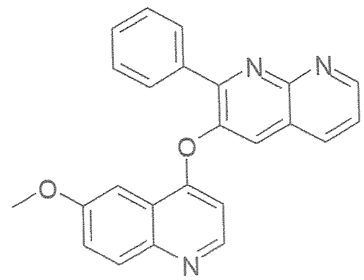
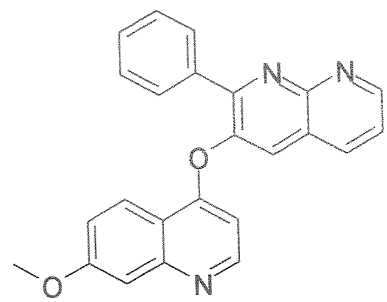
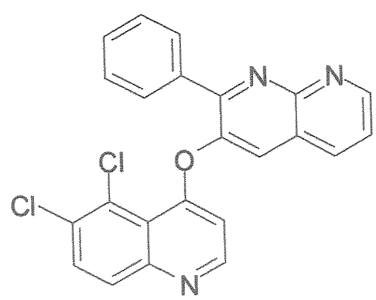
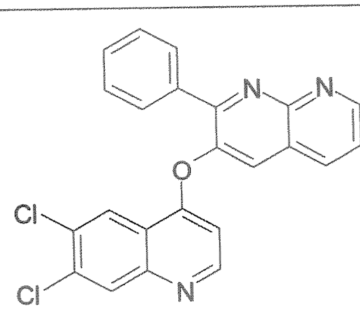
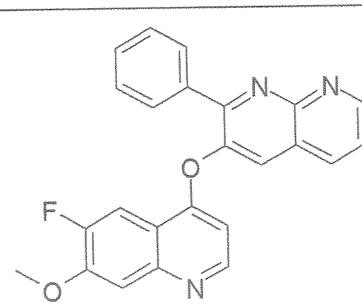
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
26		99	83	
27			100	89
28			100	96
29			100	89
30		99	84	

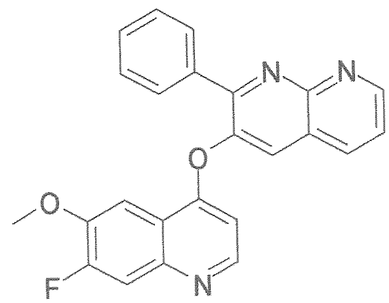
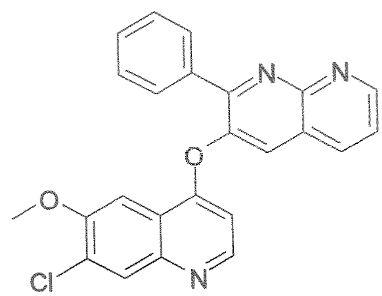
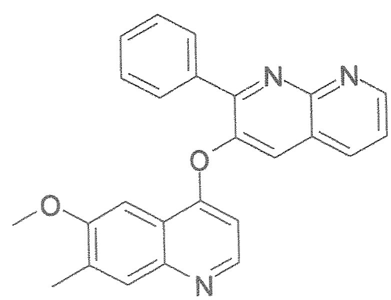
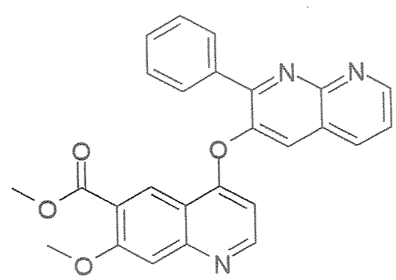
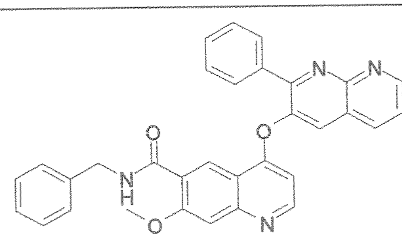
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
31		99	85	
32		94	64	
33		99	86	
34		100	94	
35		100	95	

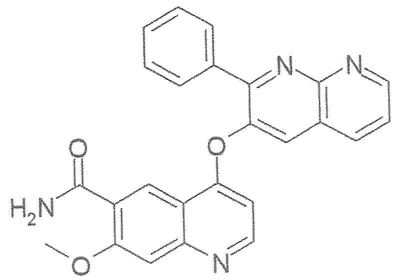
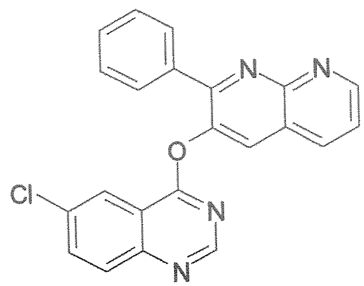
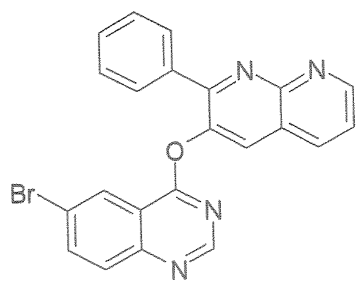
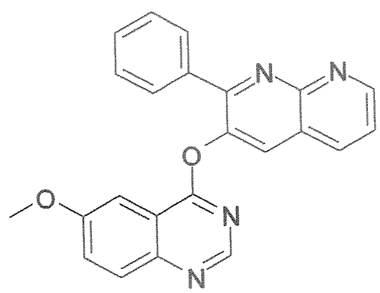
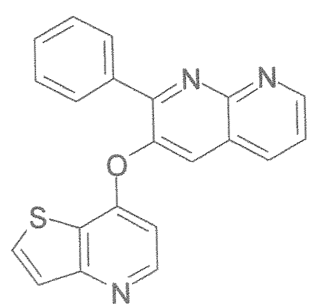
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
37			100	98
38		89	45	
39		99	88	
41		98	66	
43			84	45

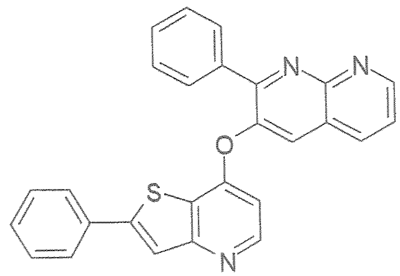
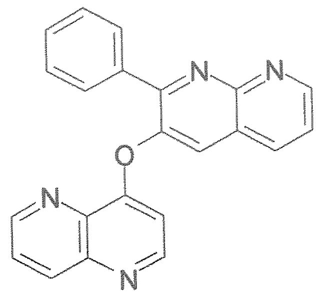
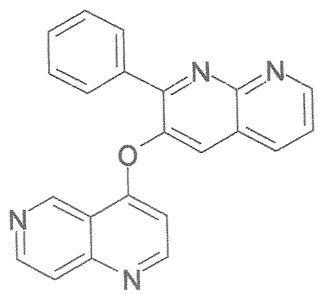
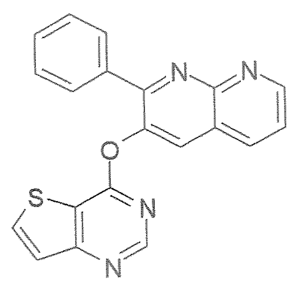
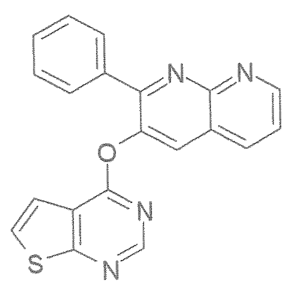
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
44		99	82	
45		100	89	
46		100	100	
48			64	28
49		100	97	

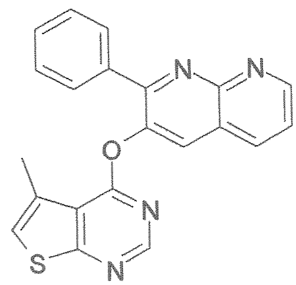
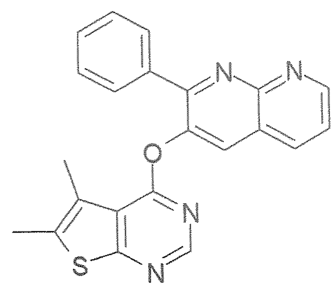
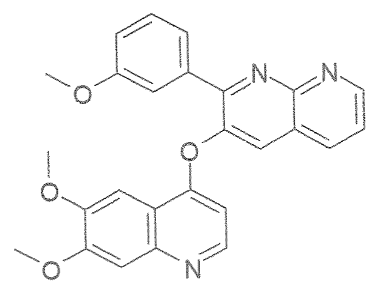
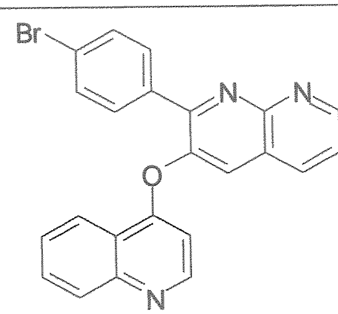
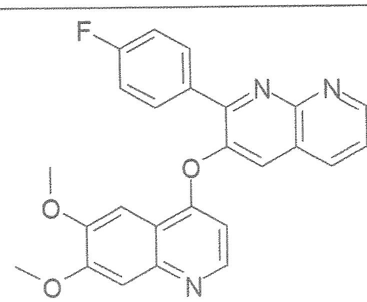
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
50		100	98	
51		100	93	
52		100	96	
53			83	43
54		99	76	

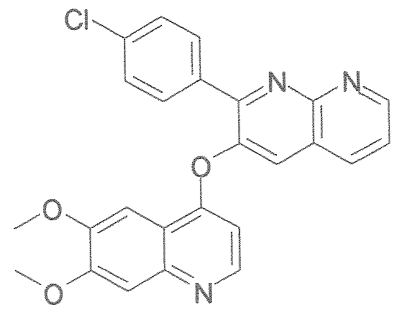
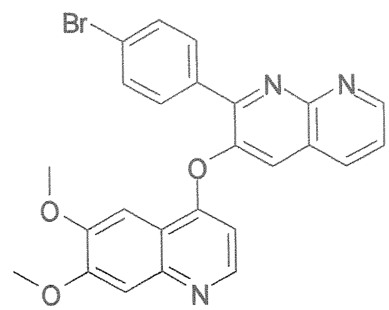
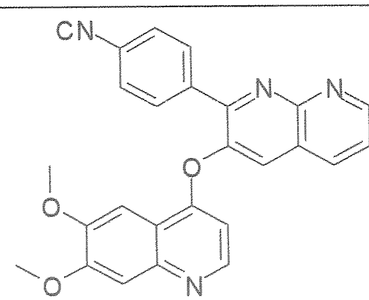
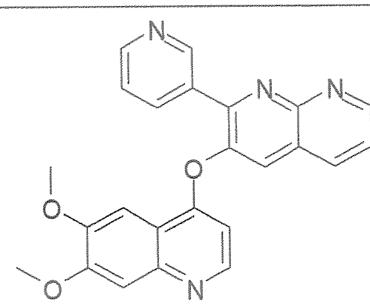
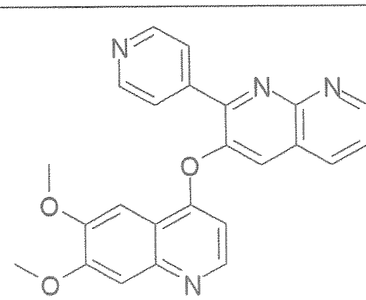
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
55		100	94	
56		100	99	
57		100	75	
58		100	83	
59				93

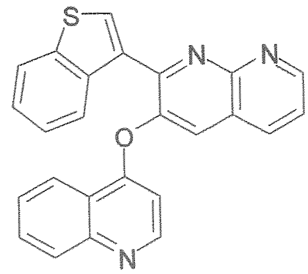
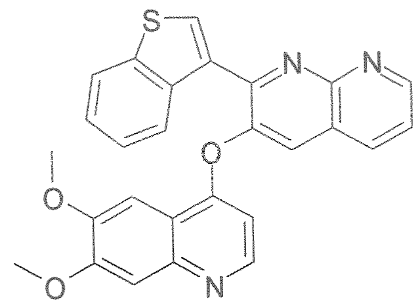
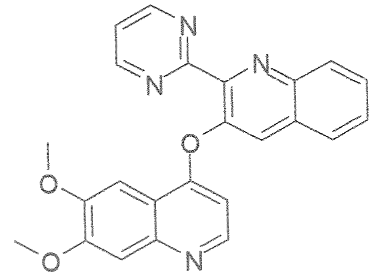
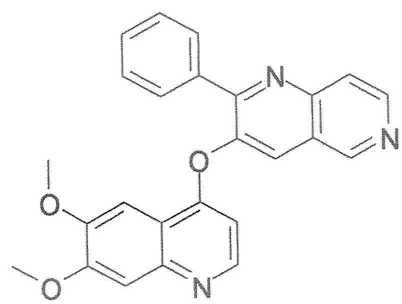
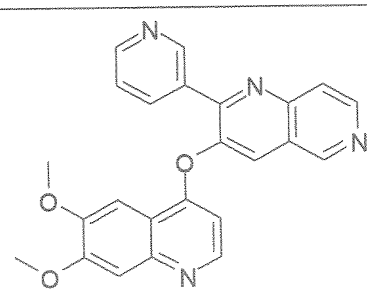
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
60		100	76	
61		100	98	
62		100	99	
63		100	99	
65		100	97	

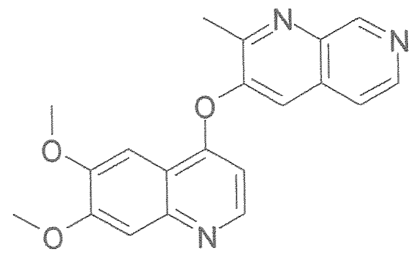
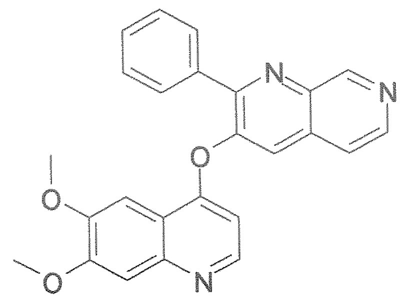
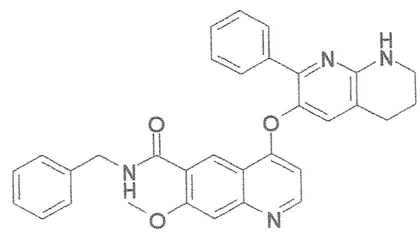
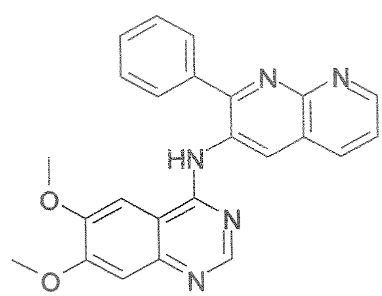
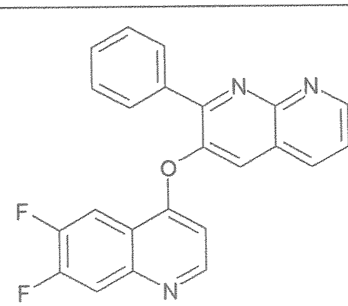
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
66			100	97
68		91	43	
69		94	52	
70		95	61	
71		100	93	

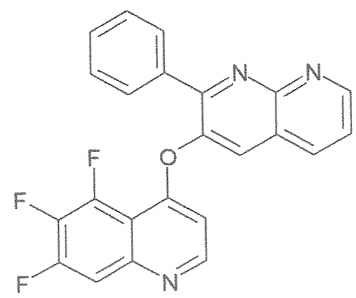
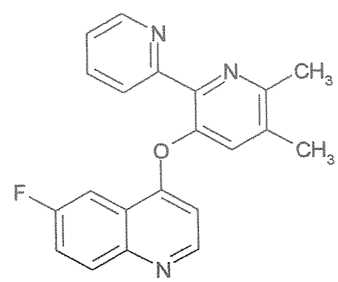
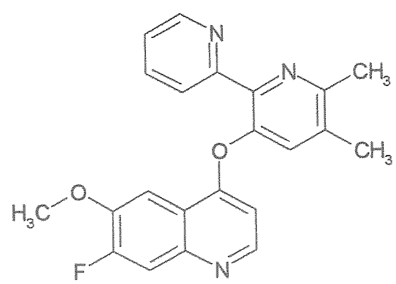
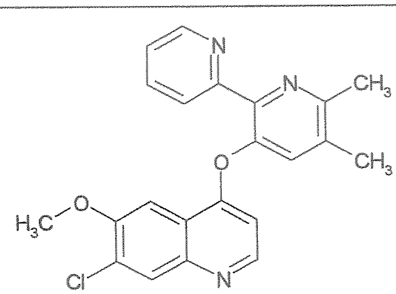
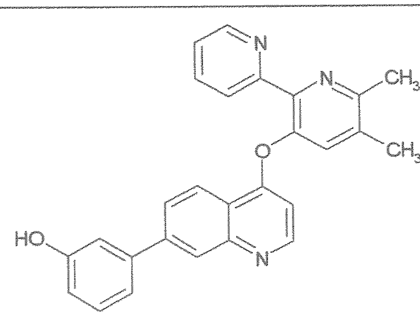
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
72			99	81
73		80	26	
74		90	53	
75		98	84	
76		83	44	

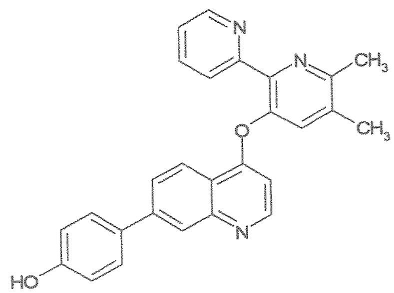
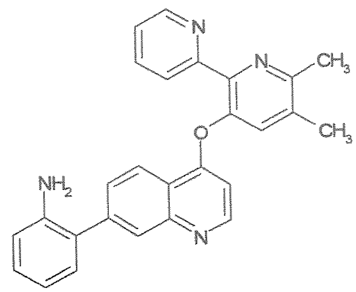
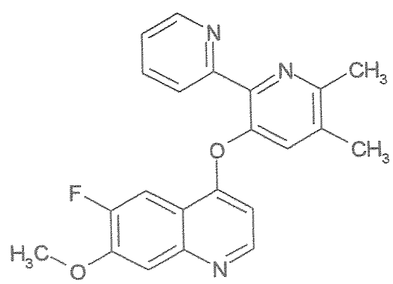
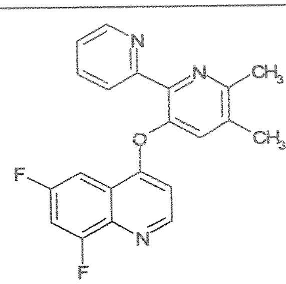
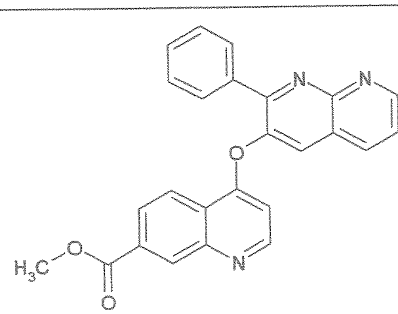
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
77		99	93	
78		99	75	
81		100	97	
82		67	25	
83		99	92	

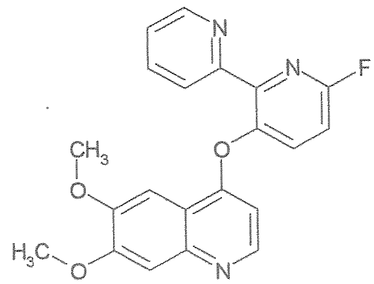
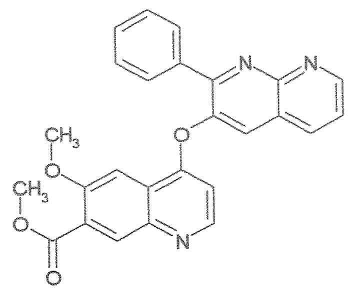
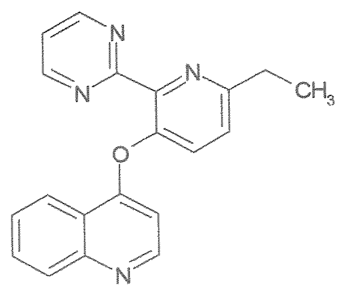
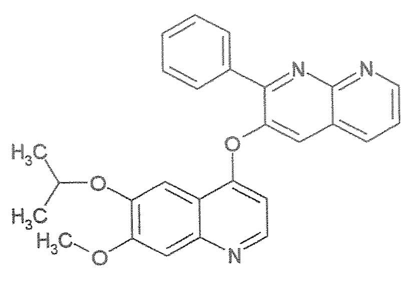
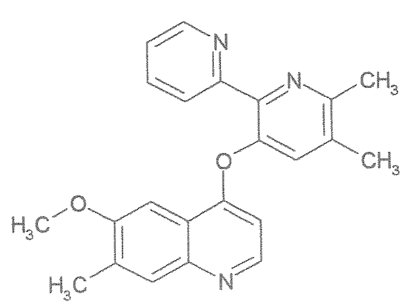
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
84		100	69	
85		97	48	
86		74	26	
88		100	90	
89		77	36	

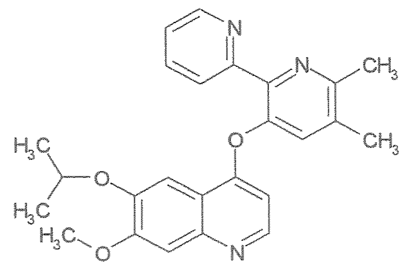
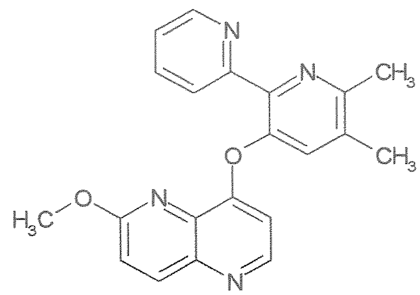
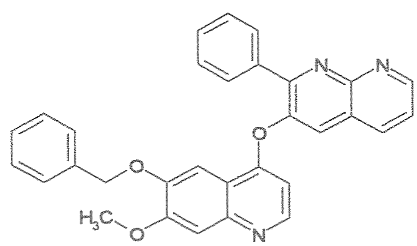
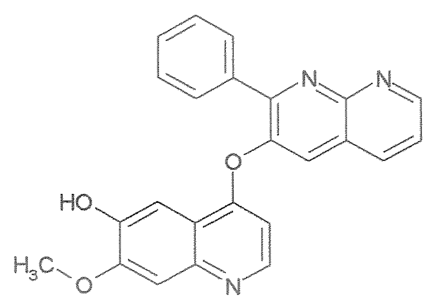
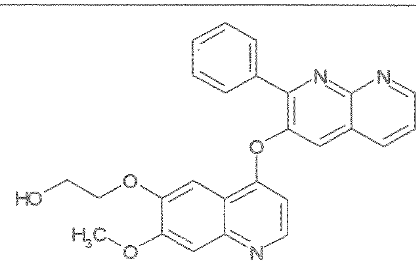
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
90		68	22	
91		100	97	
92			98	62
93		100	97	
95		85	40	

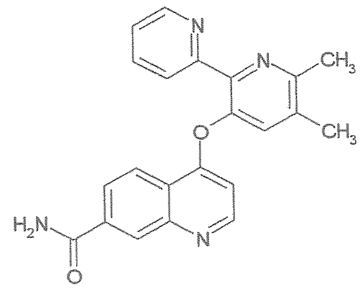
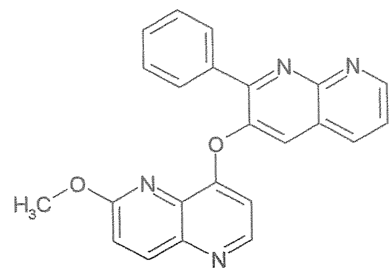
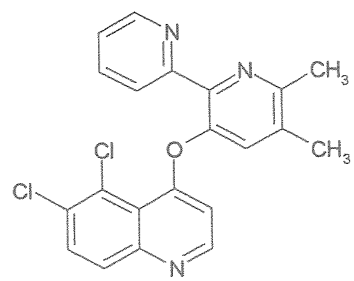
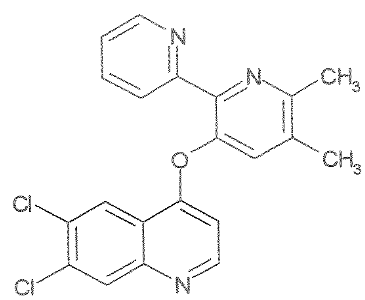
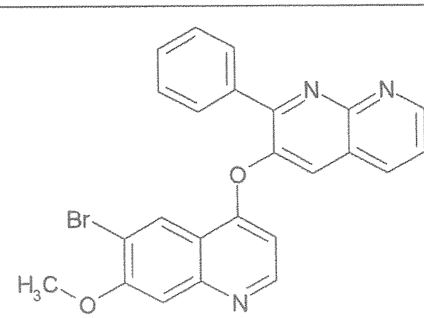
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
97		88	52	
98		100	94	
99		92	76	
100		93	56	
101		98	54	

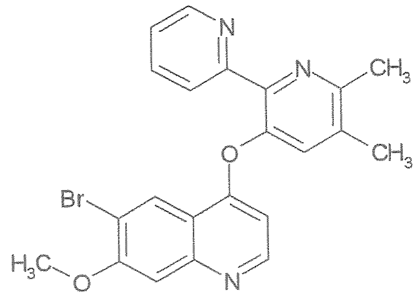
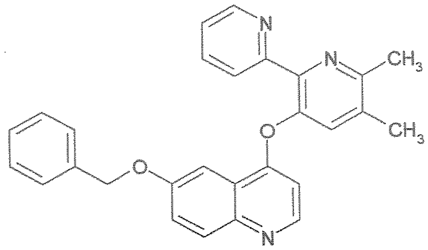
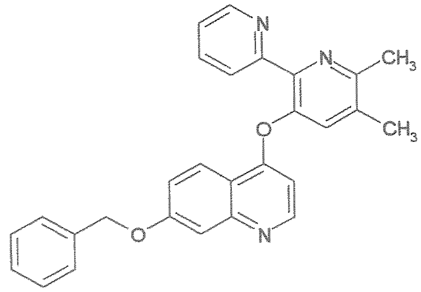
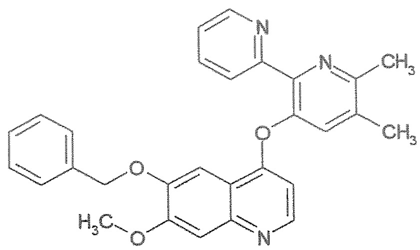
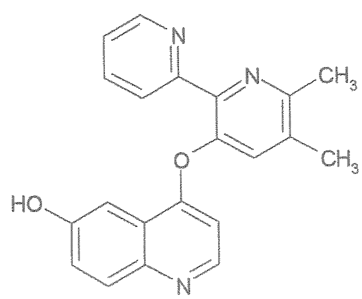
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
102		92	45	
103		100	99	
104		100	99	
105		100	100	
106		100	99	

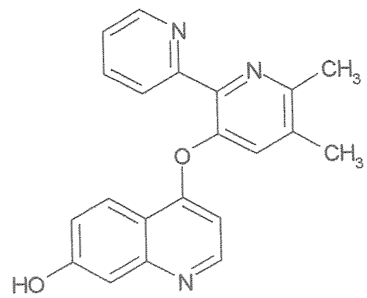
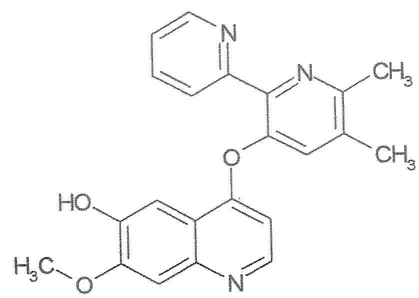
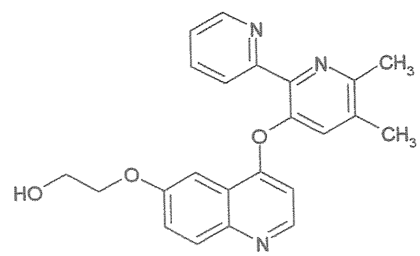
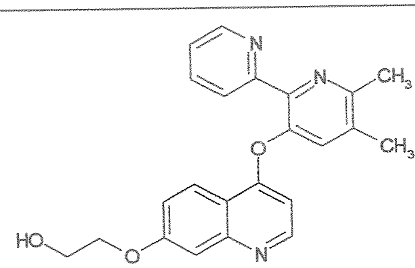
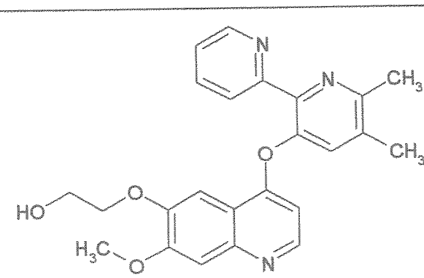
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
107		100	100	
108		100	96	
110		100	100	
111		84	43	
113		100	95	

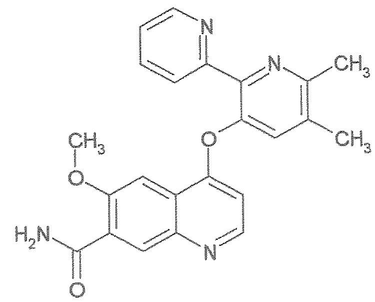
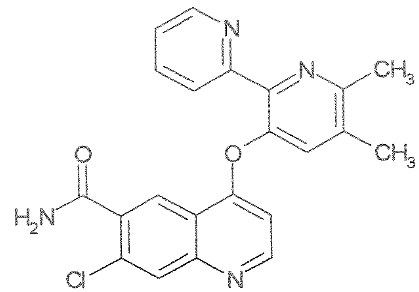
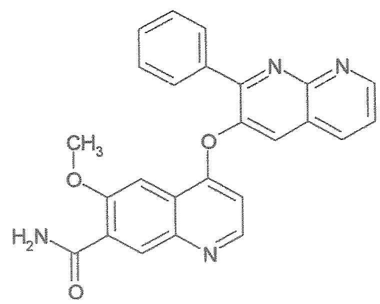
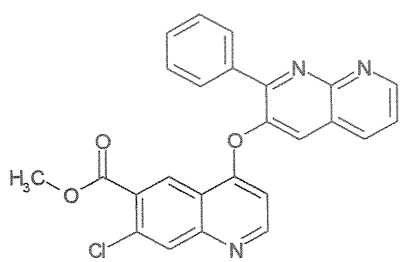
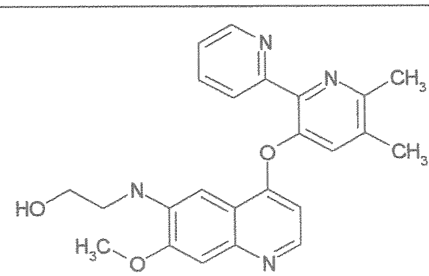
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
115		100	100	
116		100	99	
117		100	96	
118		100	100	
119		100	100	

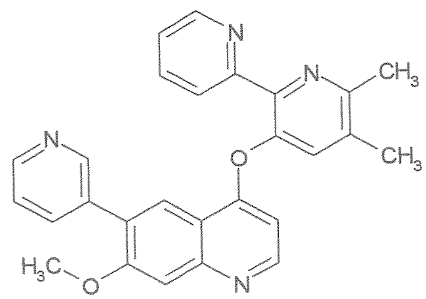
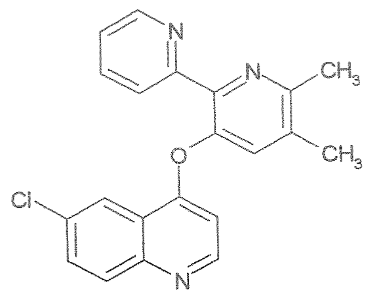
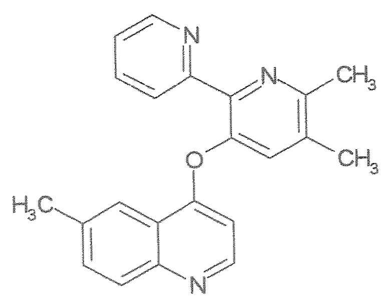
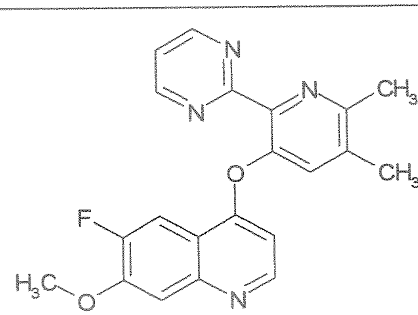
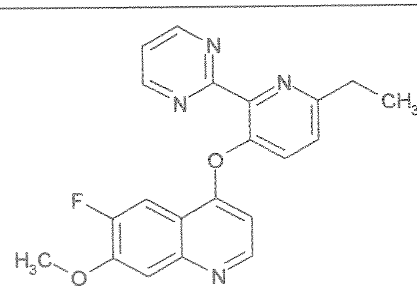
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
120		100	94	
121		100	98	
123		100	99	
124		100	99	
125		100	99	

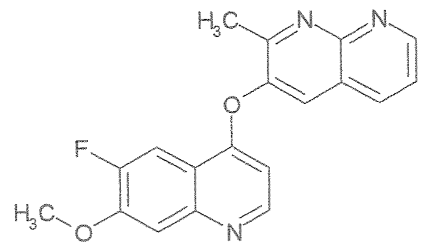
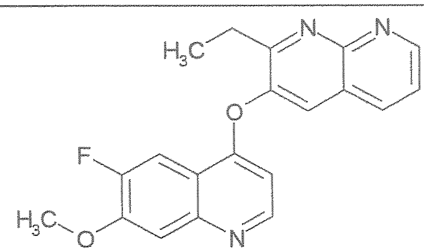
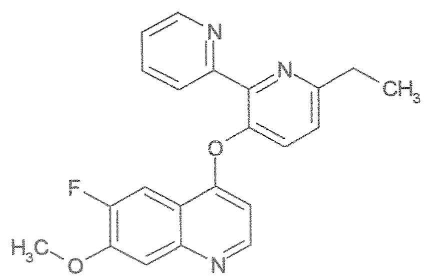
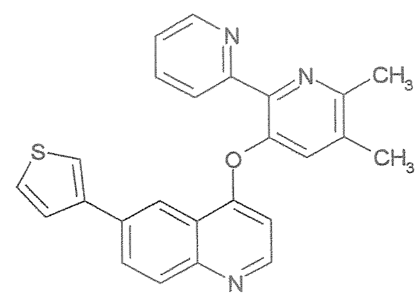
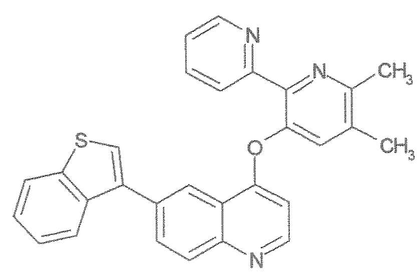
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
126		100	93	
128		100	93	
130		100	100	
131		100	99	
132		100	98	

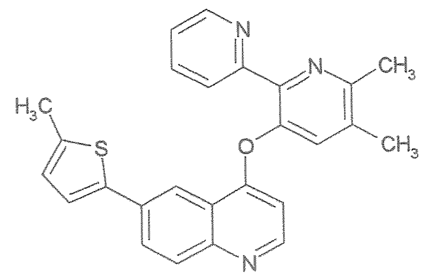
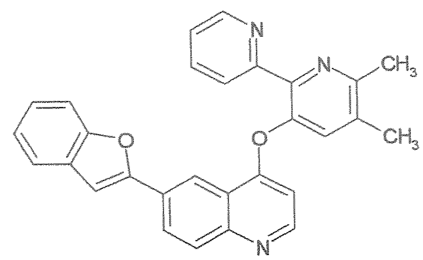
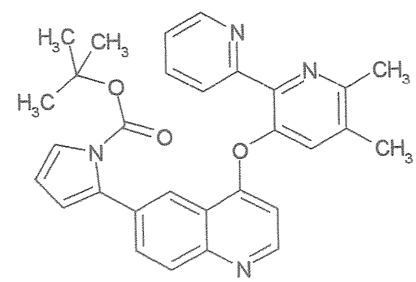
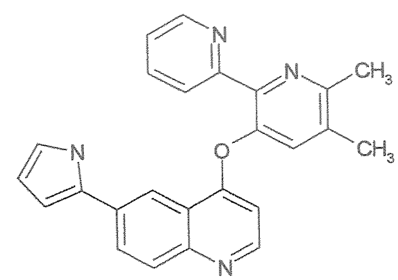
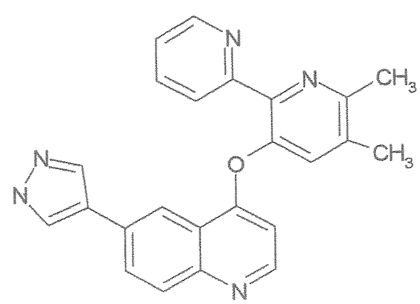
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
133		100	99	
136		100	93	
137		100	88	
138		100	98	
139		100	100	

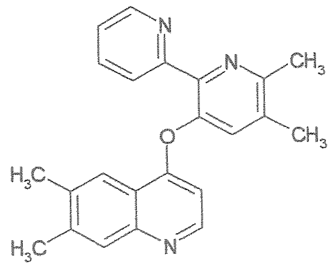
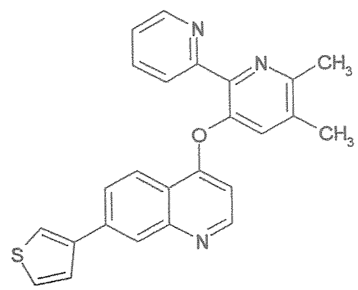
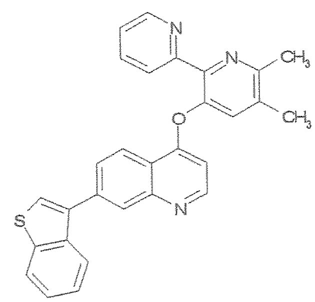
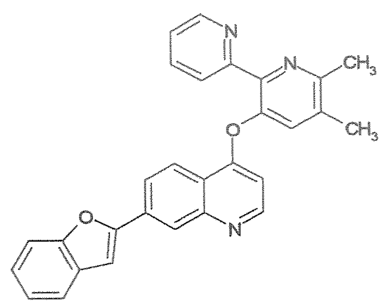
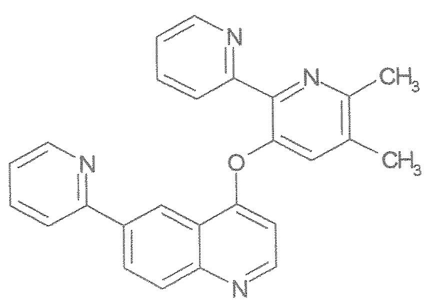
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
140		100	99	
141		100	100	
142		100	98	
143		100	100	
144		100	93	

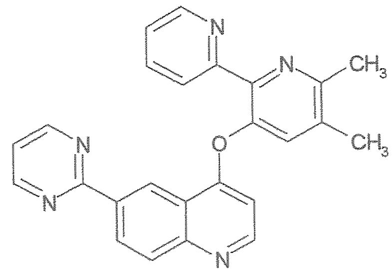
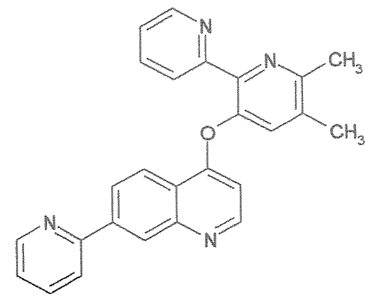
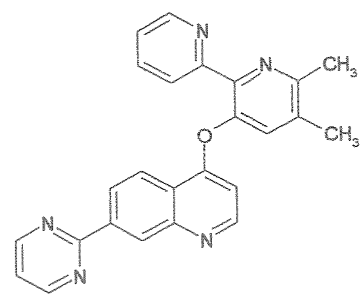
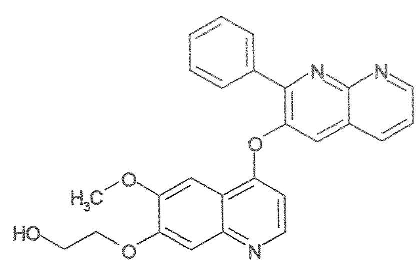
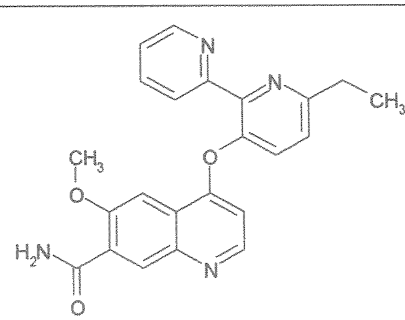
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
145		100	78	
146		95	54	
147		77	34	
148		98	58	
154		100	99	

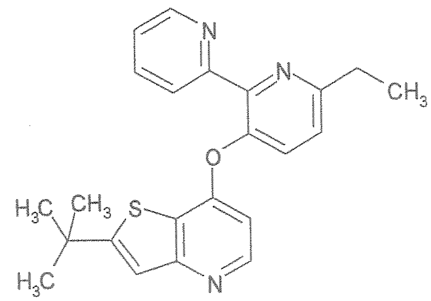
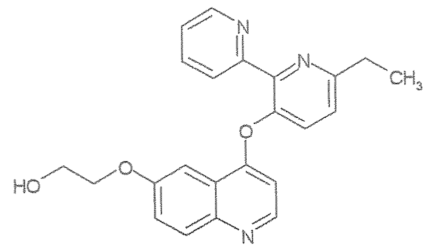
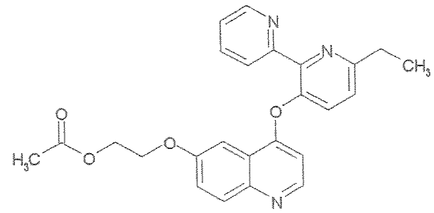
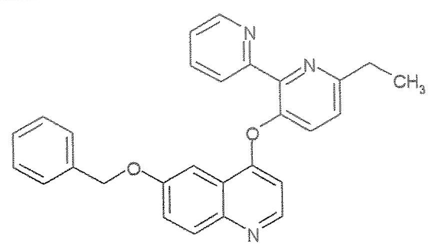
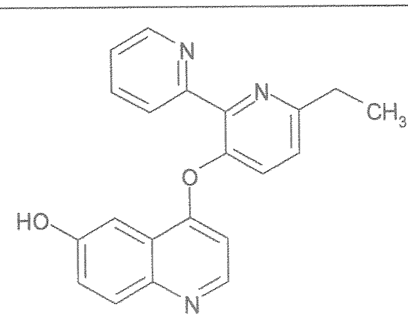
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
155		100	99	
156		100	100	
157		100	99	
158		100	98	
159		100	99	

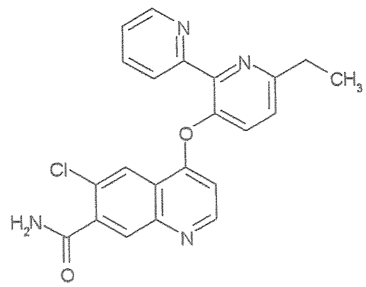
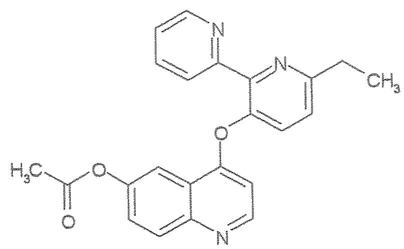
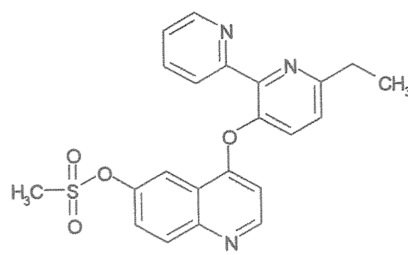
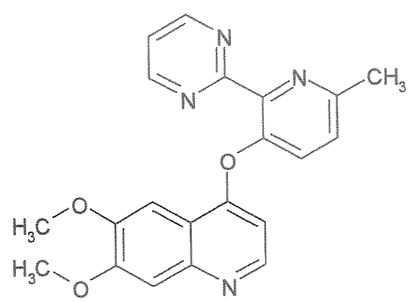
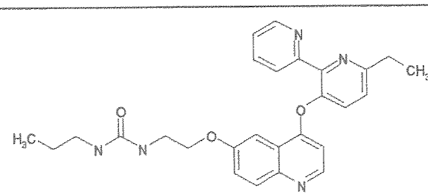
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
160		87	56	
161		95	68	
162		100	100	
163		100	92	
164		100	75	

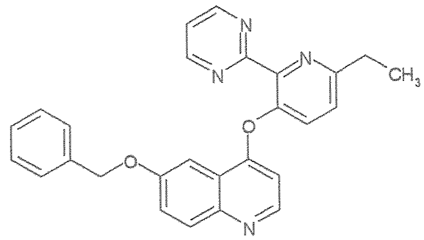
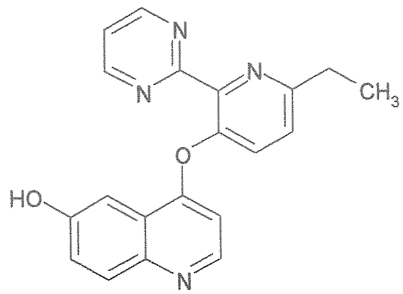
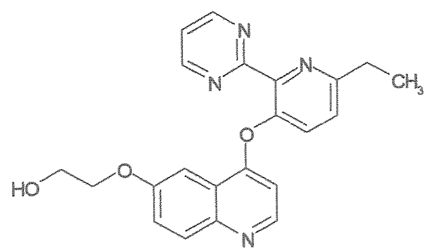
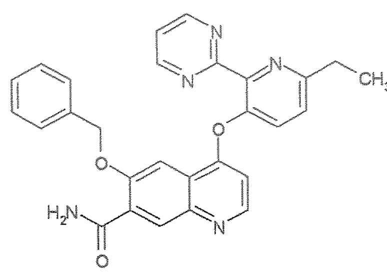
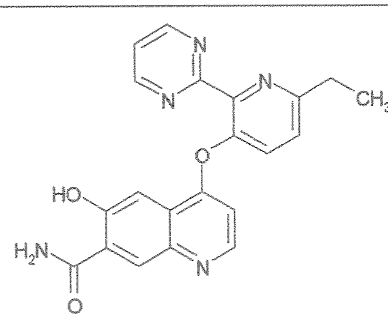
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
165		100	90	
166		100	78	
167		85	35	
168		100	92	
169		100	100	

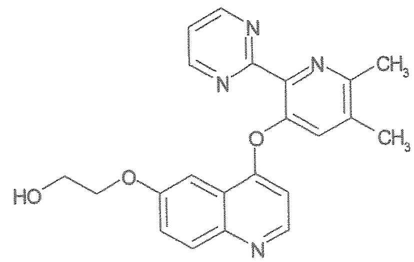
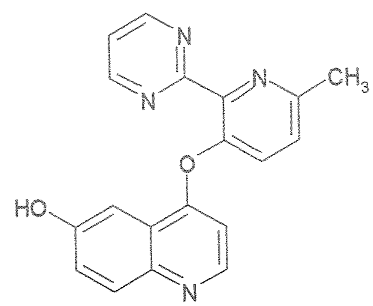
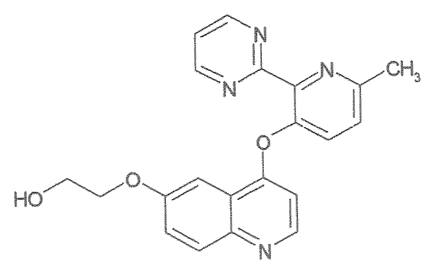
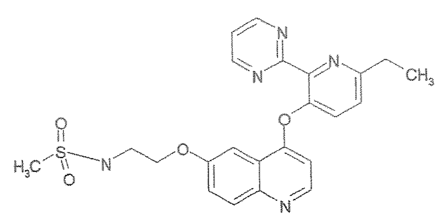
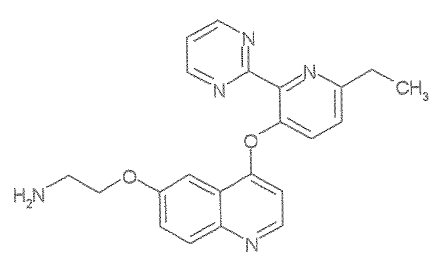
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
170		100	98	
171		100	100	
172		90	49	
173		92	57	
174		100	89	

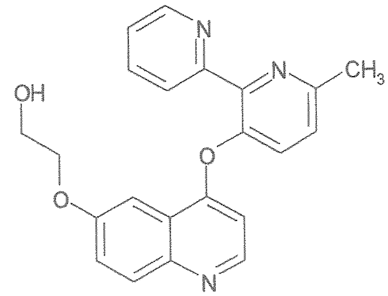
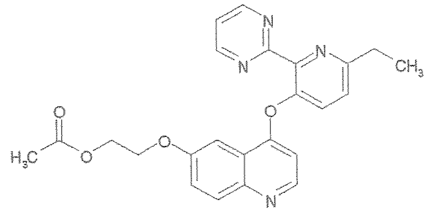
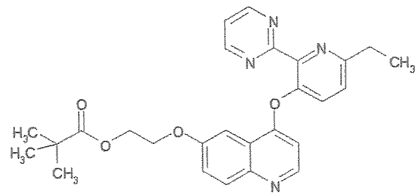
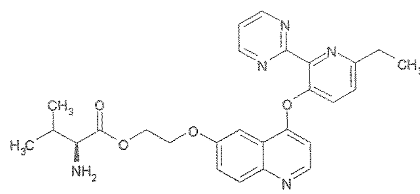
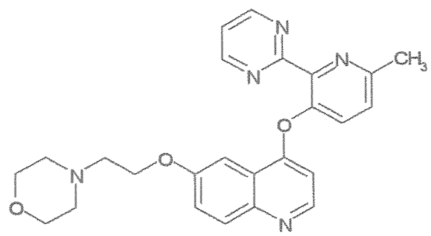
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
175		100	97	
176		100	99	
177		100	98	
178		100	100	
179		100	100	

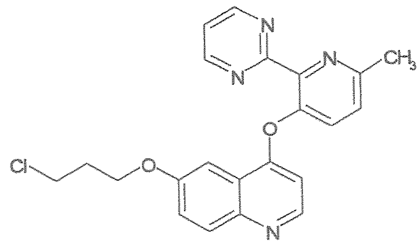
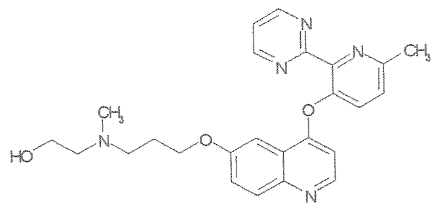
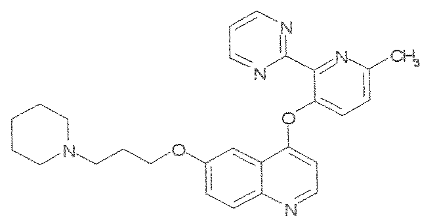
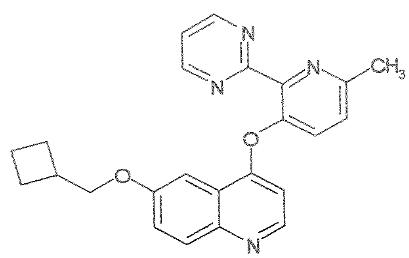
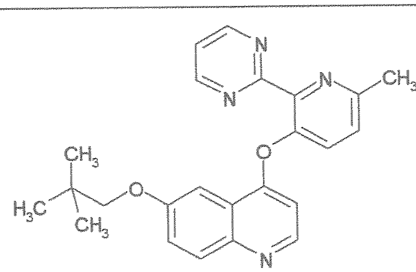
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
180		98	74	
181		100	100	
182		100	99	
183		100	100	
184		100	100	

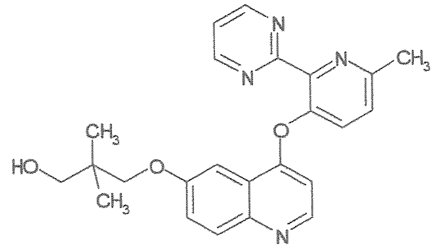
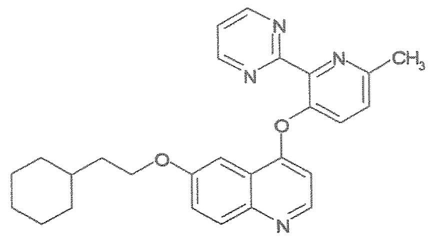
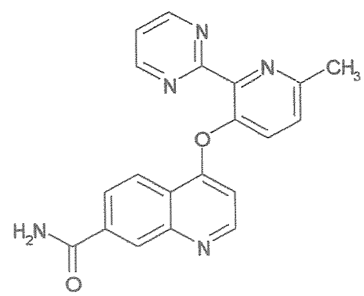
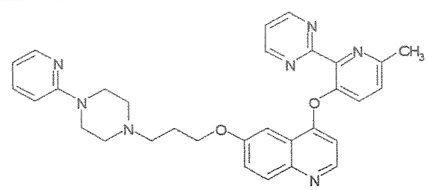
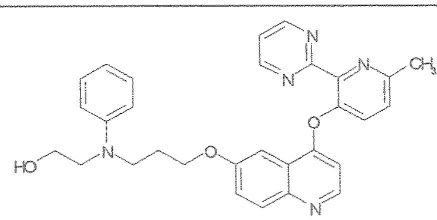
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
185		100	96	
186		100	100	
187		100	100	
188		100	100	
189		99	97	

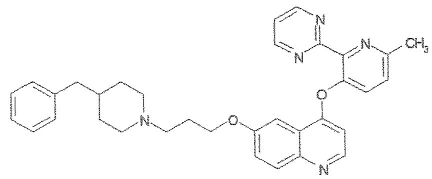
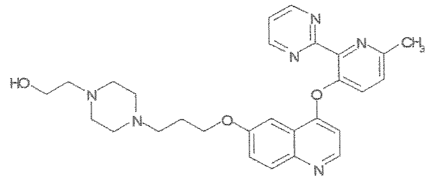
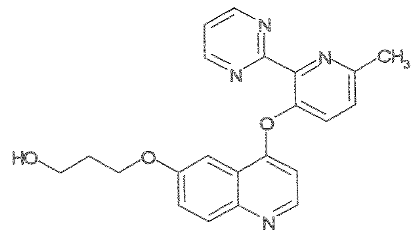
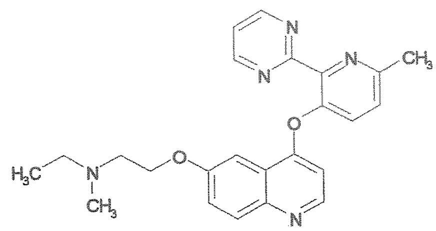
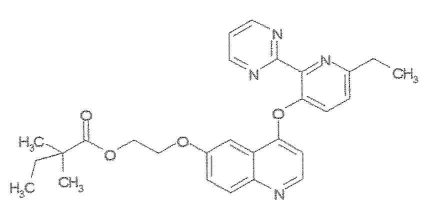
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
190		100	100	
191		100	99	
192		100	97	
193			80	
194			60	

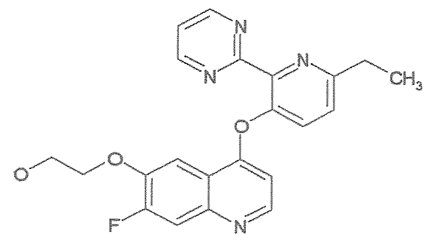
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
200			85	
201			82	
202			86	
203			79	
204			84	

Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
205			98	
206			89	
207			93	
208			75	
209			54	

Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
210			87	
211			54	
212			55	
213			98	
214			90	

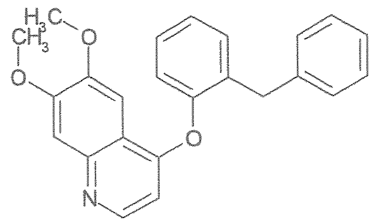
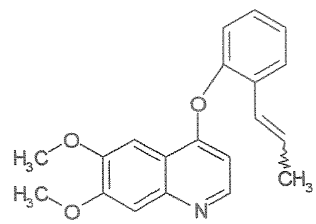
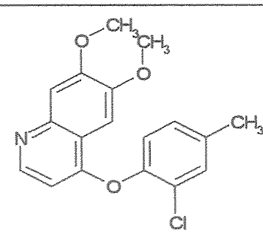
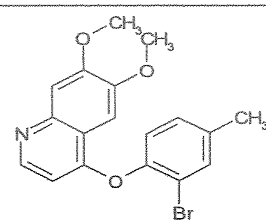
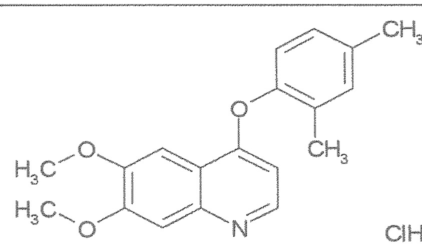
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
215			79	
216			84	
217		100	90	
218		100	84	
219		100	96	

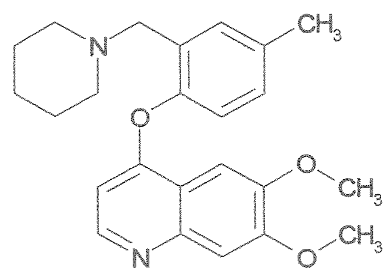
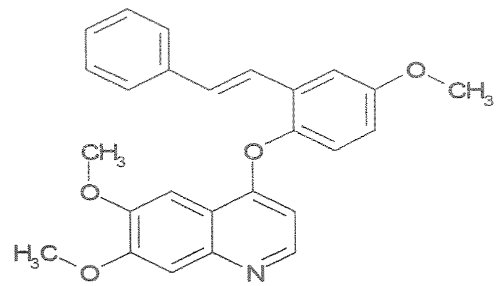
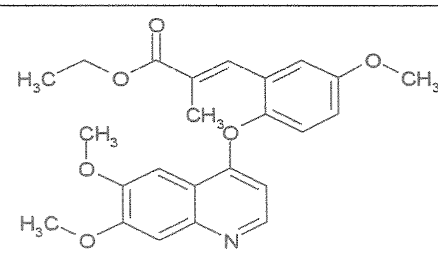
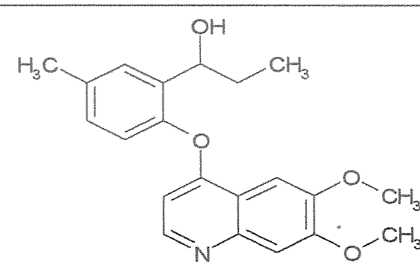
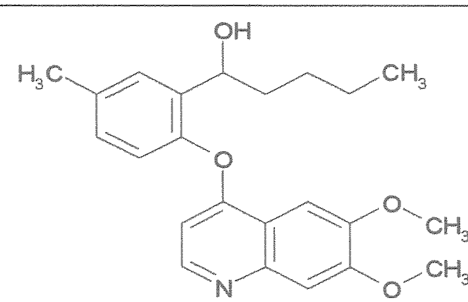
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
220		100	91	
221		79	39	
222		100	91	
223		90	52	
224		100	95	

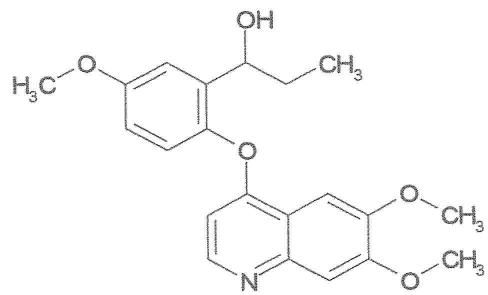
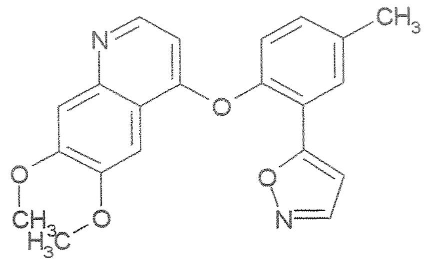
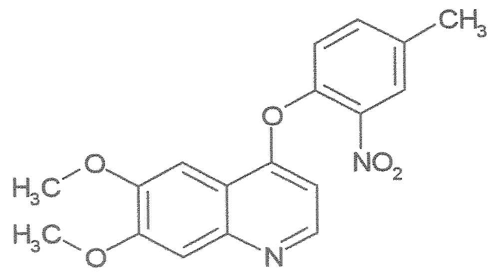
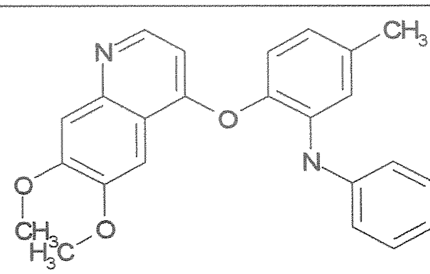
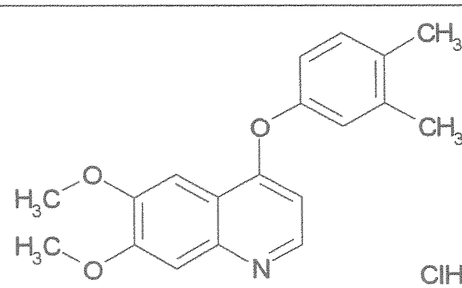
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
225		99	89	

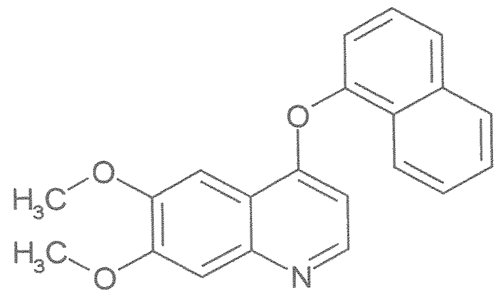
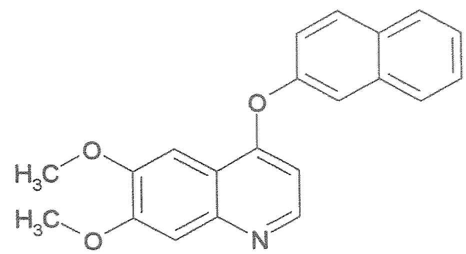
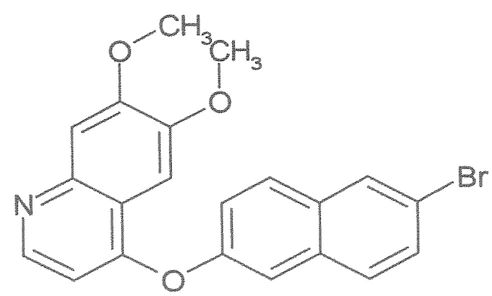
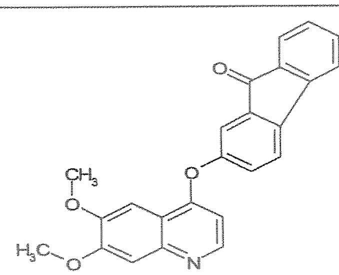
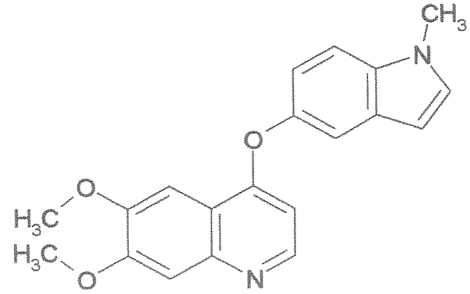
[0540] Table 1B:

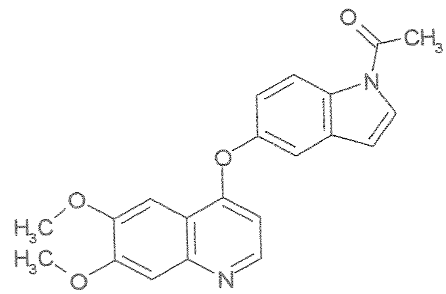
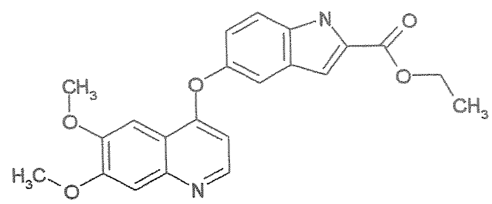
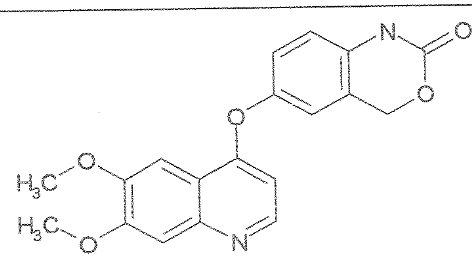
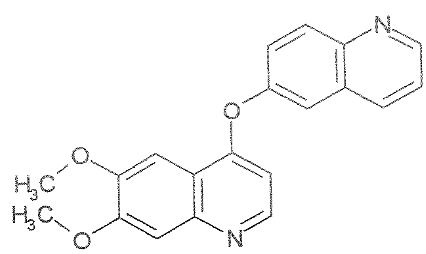
[Table 1B]

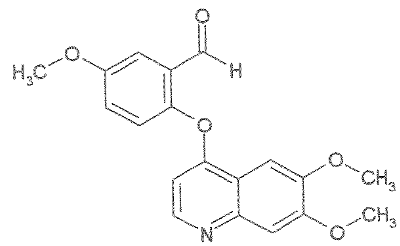
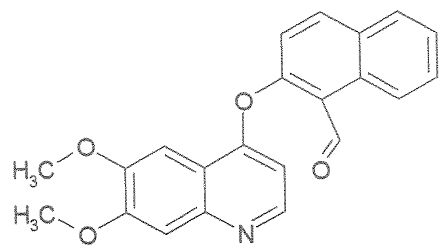
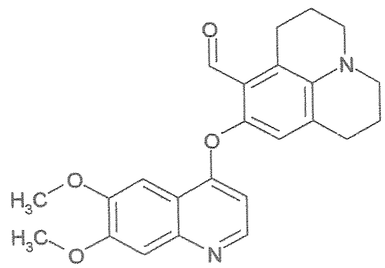
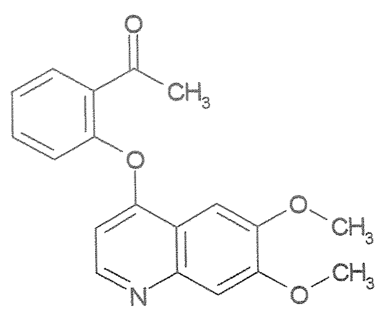
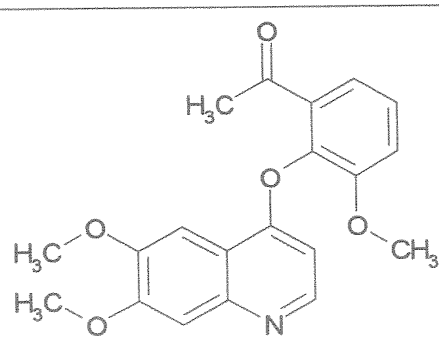
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 1		53	5
r 2		88	13
r 3		75	0
r 4		78	20
r 5		56	13

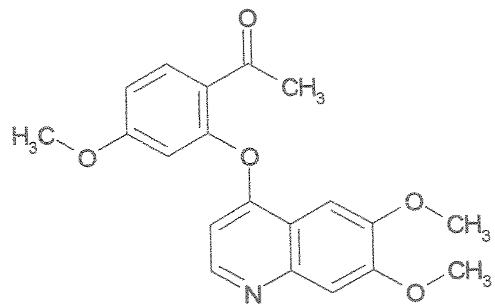
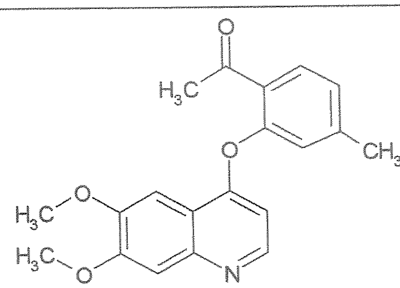
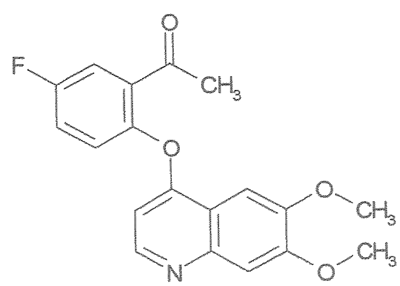
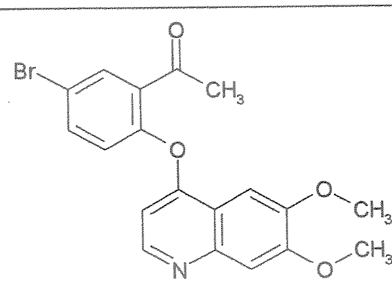
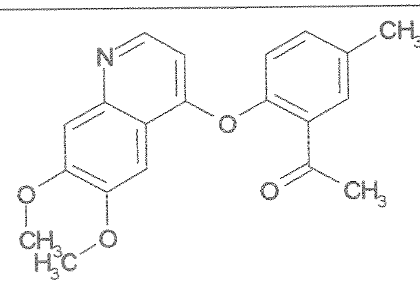
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 6		72	30
r 7		54	13
r 8		59	10
r 9		77	29
r 10		87	38

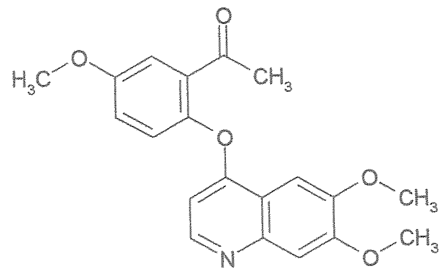
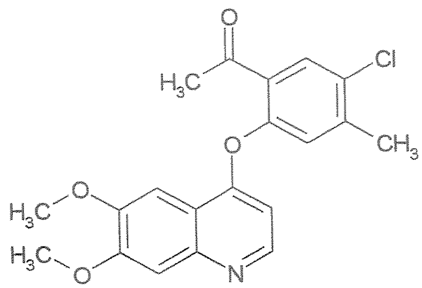
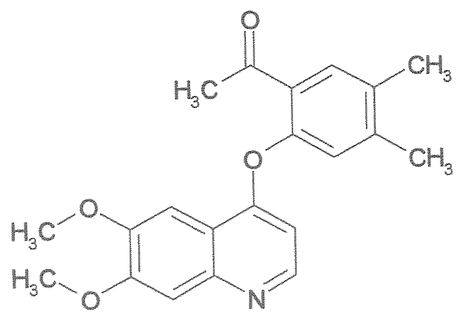
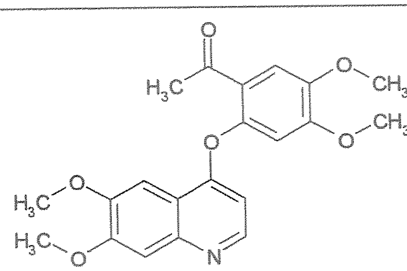
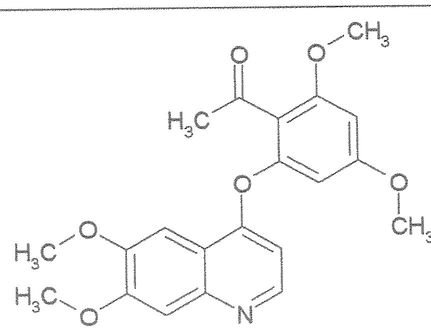
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 11		66	28
r 12		89	21
r 13		78	28
r 14		64	15
r 15		84	41

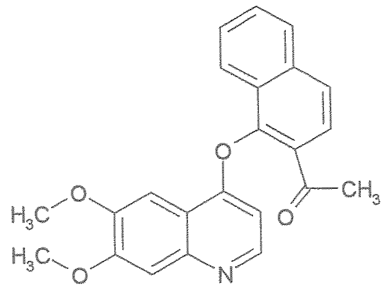
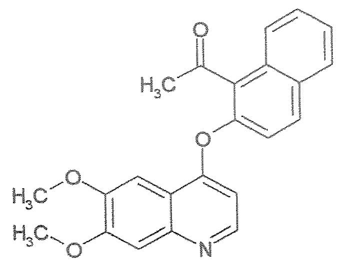
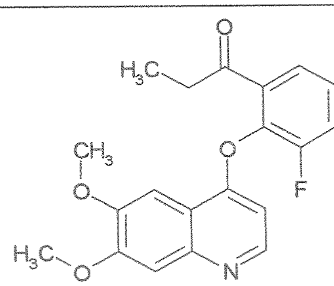
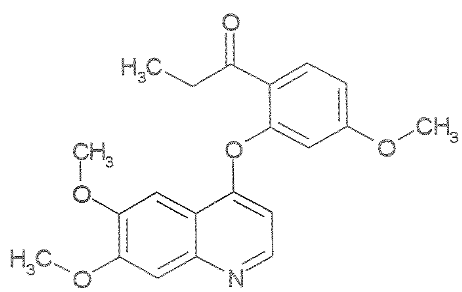
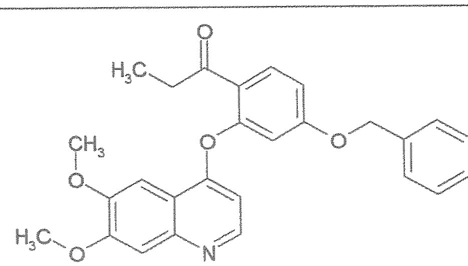
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 16		62	0
r 17		80	15
r 18		69	15
r 19		95	73
r 20		69	19

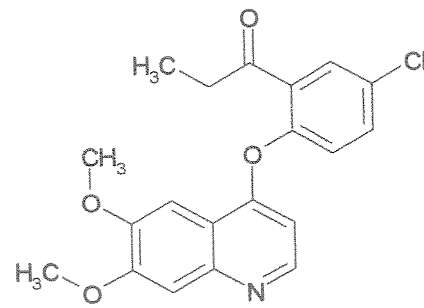
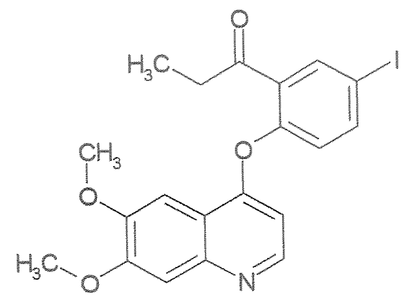
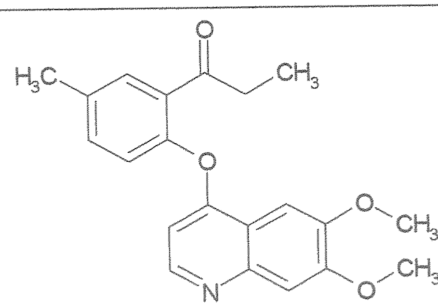
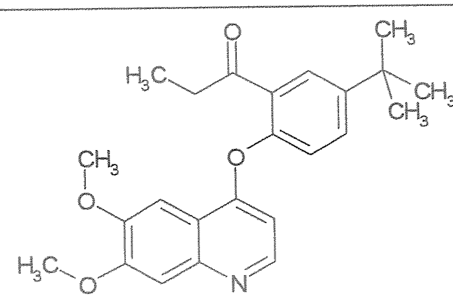
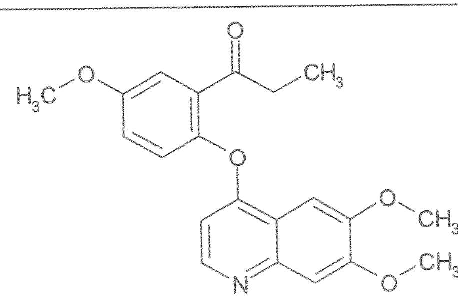
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 21		71	16
r 22		81	11
r 23		91	56
r 24		91	66
r 25			

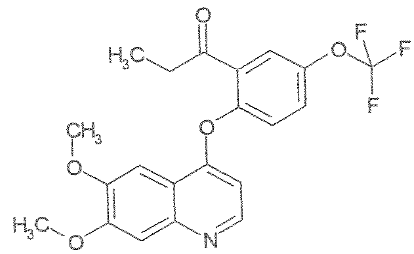
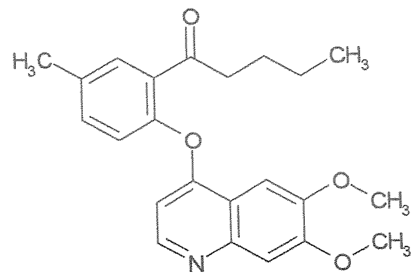
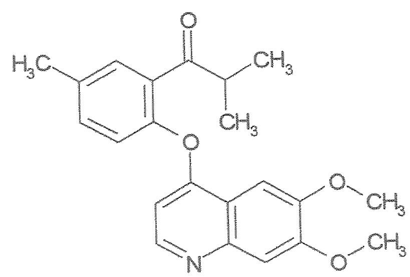
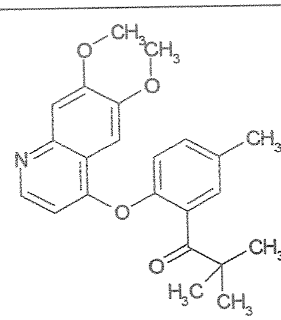
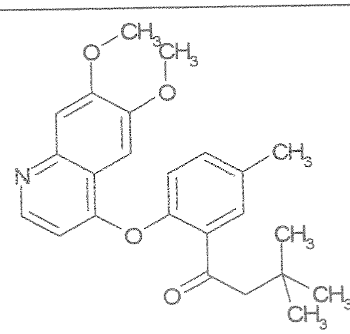
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 26		73	20
r 27		93	0
r 28		53	0
r 29		67	0
r 30		61	0

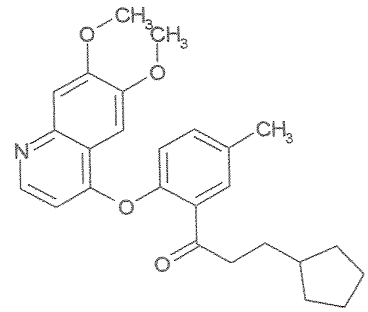
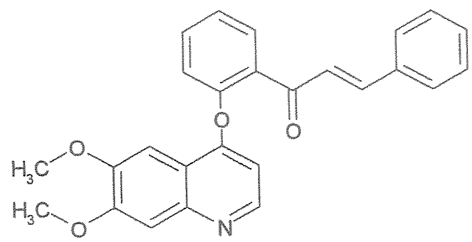
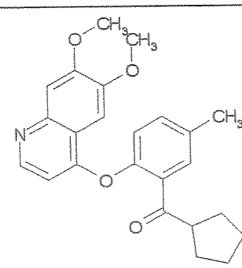
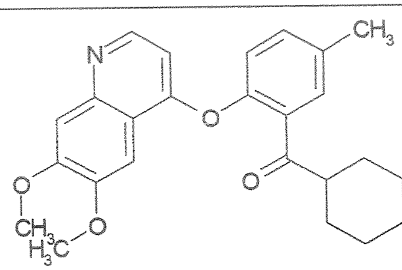
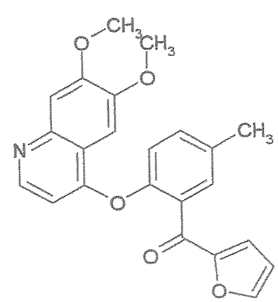
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 31		98	49
r 32		98	81
r 33		94	27
r 34		78	0
r 35		89	49

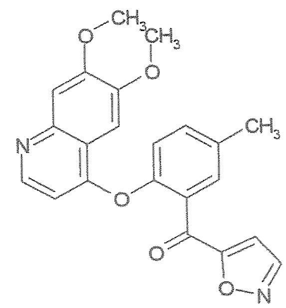
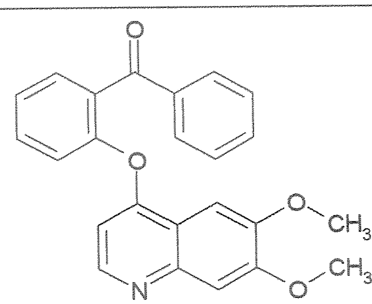
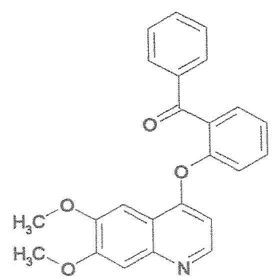
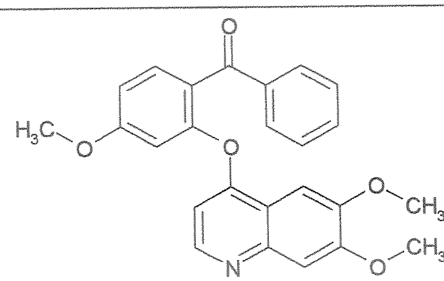
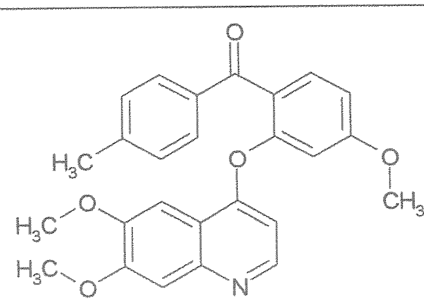
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 36		100	95
r 37		100	94
r 38		100	98
r 39		91	0
r 40		83	12

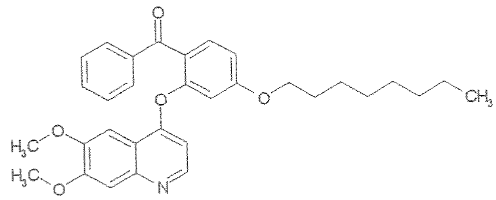
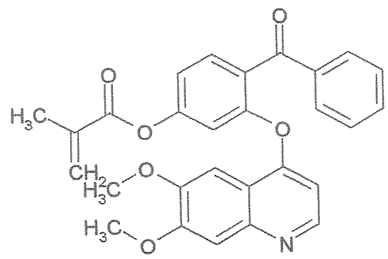
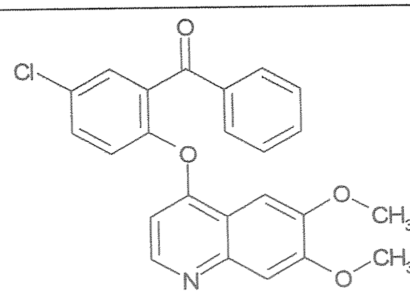
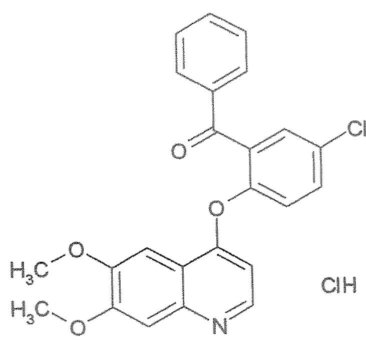
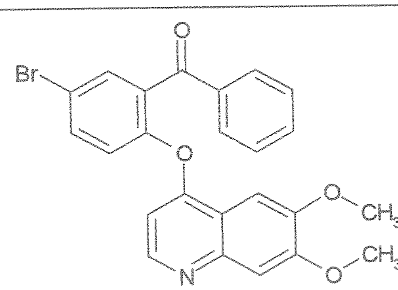
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 41		97	57
r 42		93	90
r 43		66	0
r 44		100	97
r 45		67	0

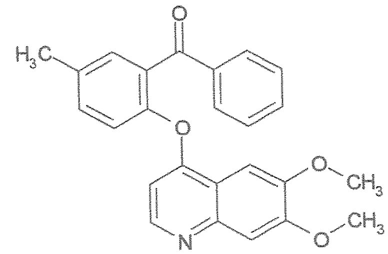
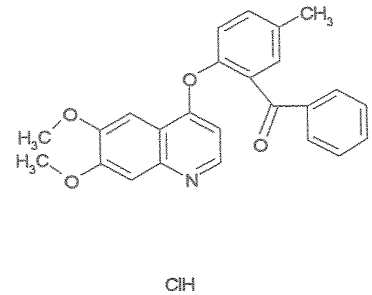
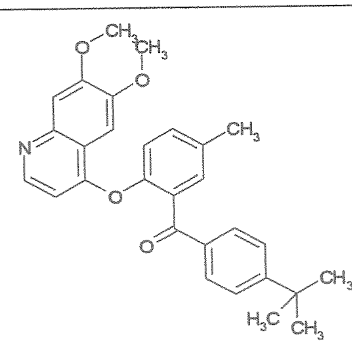
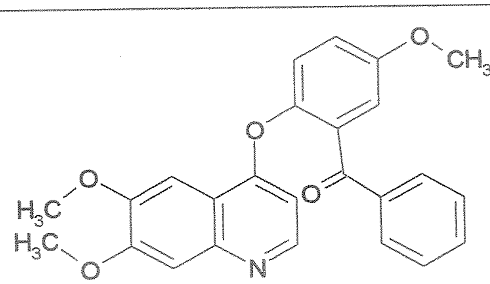
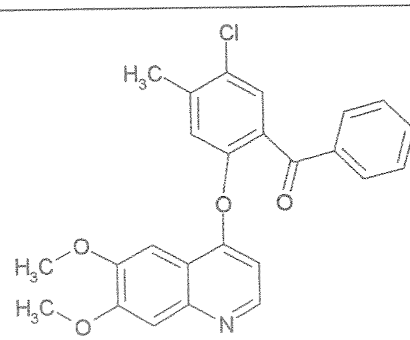
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 46		100	70
r 47		98	45
r 48		100	98
r 49		62	0
r 50		100	100

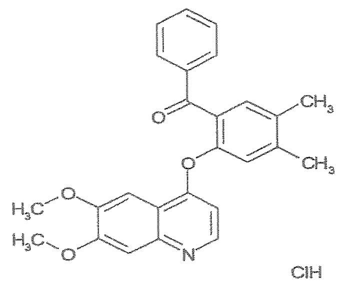
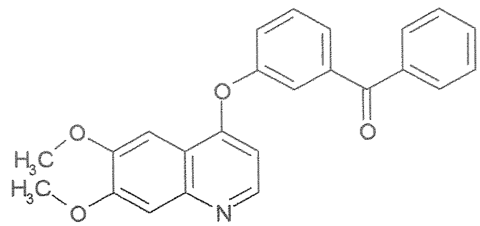
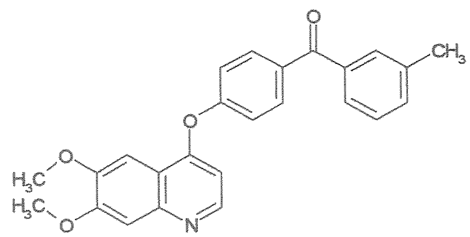
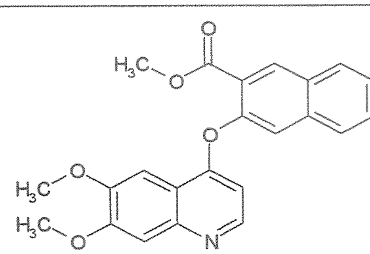
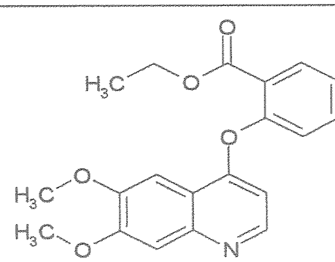
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 51		99	71
r 52		100	97
r 53		100	97
r 54		73	13
r 55		98	53

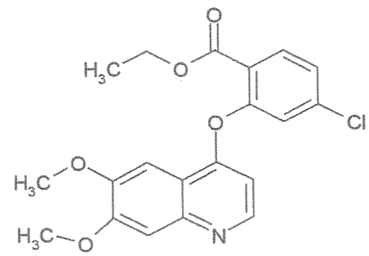
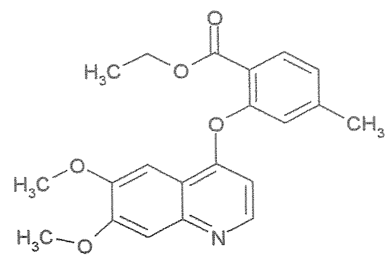
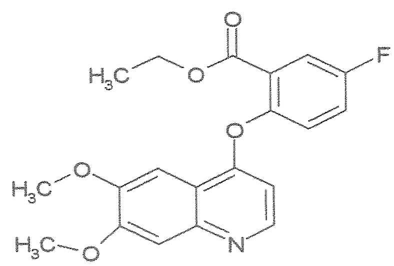
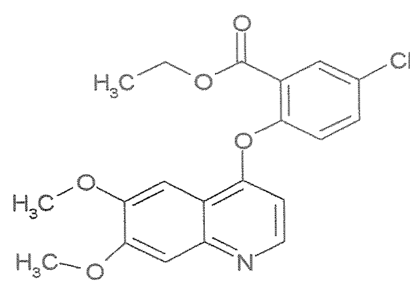
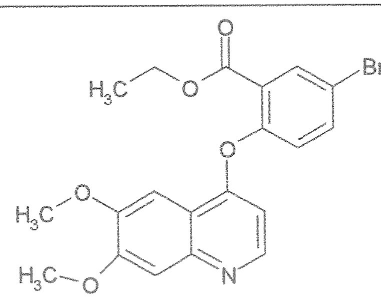
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 56		84	0
r 57		55	10
r 58		100	90
r 59		99	65
r 60		98	63

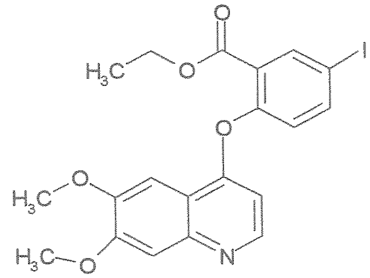
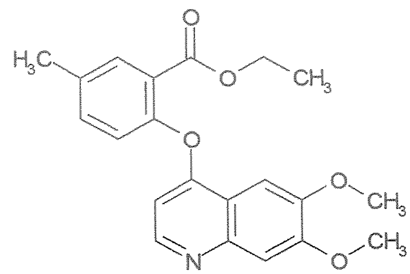
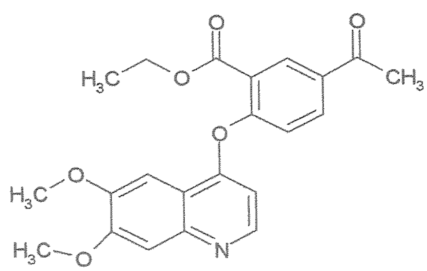
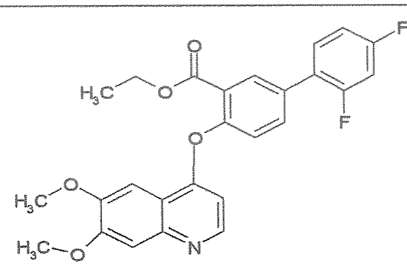
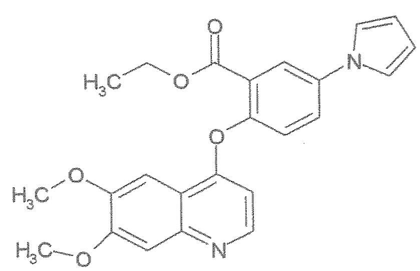
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 61		98	61
r 62		85	43
r 63	 ClH	91	57
r 64		98	67
r 65		100	58

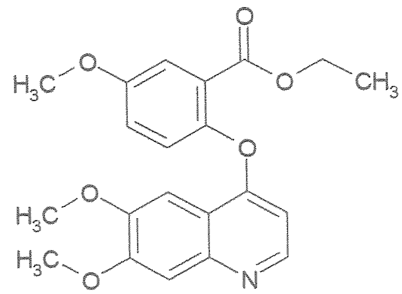
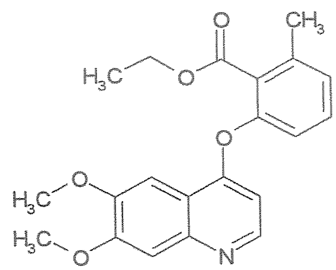
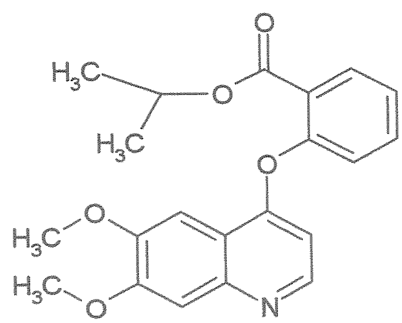
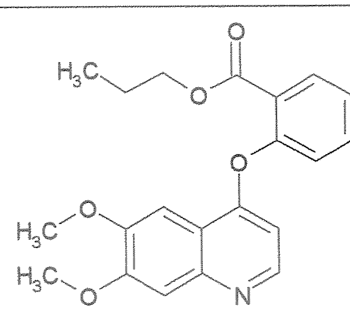
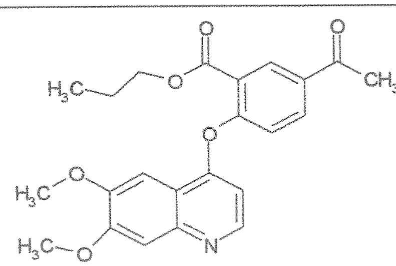
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 66		86	22
r 67		93	4
r 68		100	89
r 69		100	100
r 70		100	73

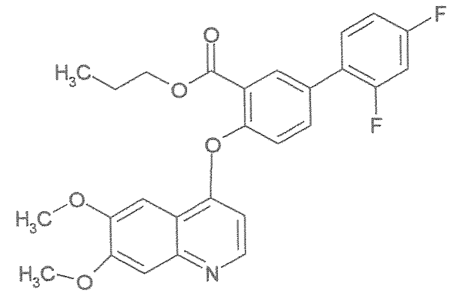
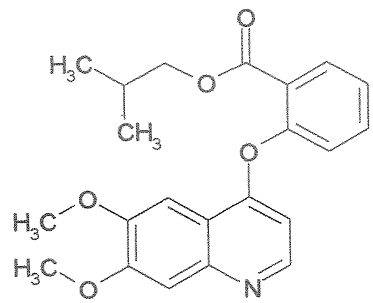
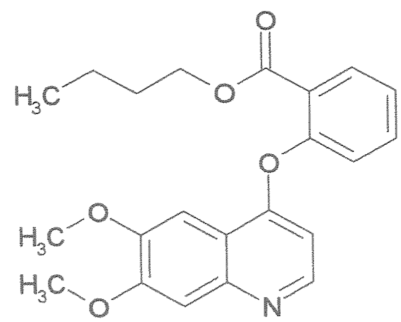
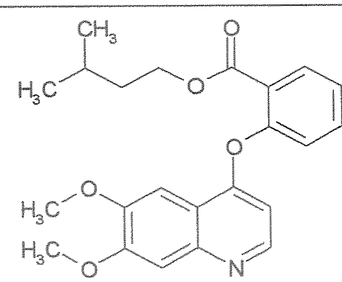
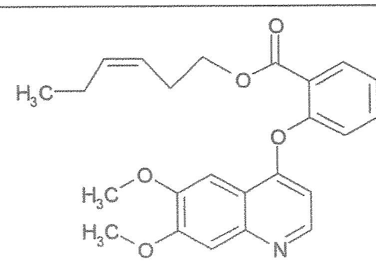
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 71		100	79
r 72		100	98
r 73		81	24
r 74		84	27
r 75		100	97

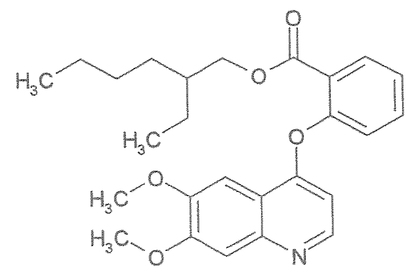
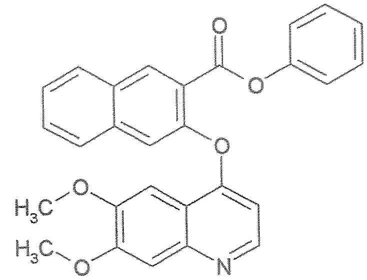
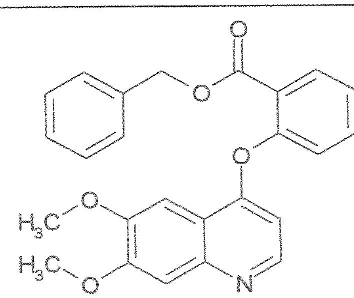
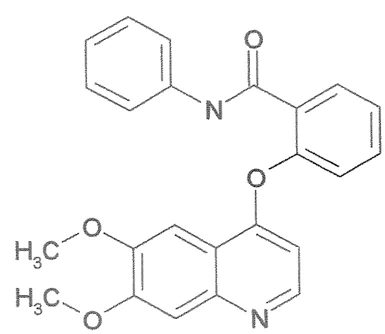
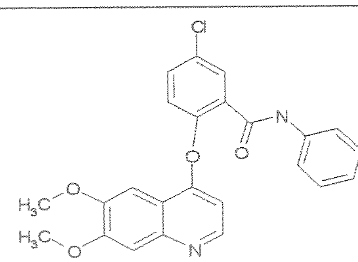
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 76		100	95
r 77		46	0
r 78		57	0
r 79		100	97
r 80		95	62

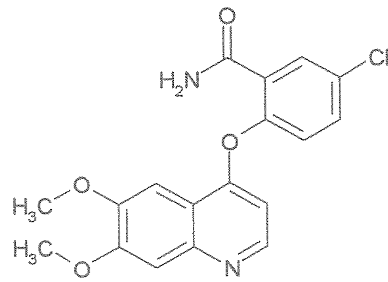
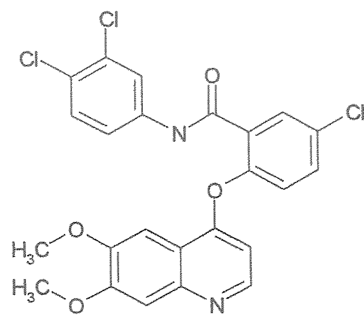
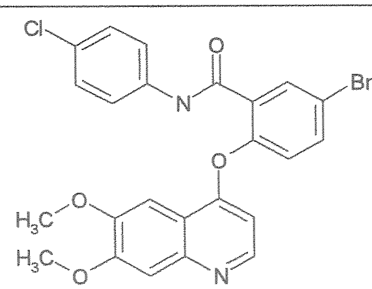
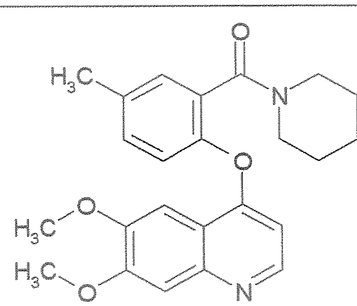
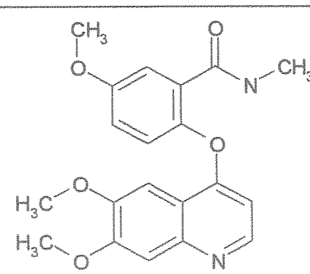
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 81		100	91
r 82		99	90
r 83		81	41
r 84		100	84
r 85		100	87

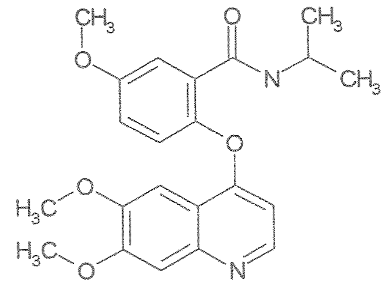
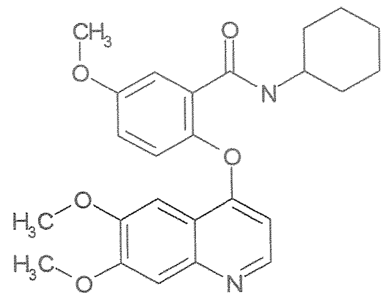
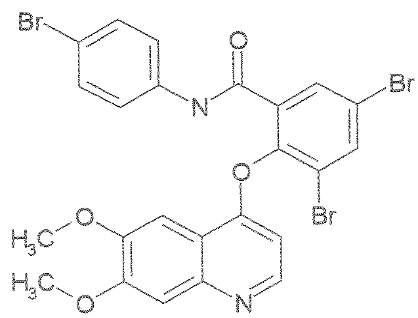
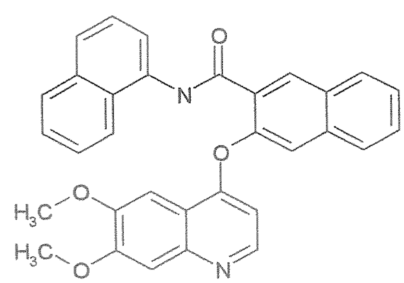
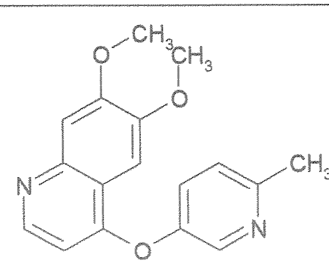
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 86		99	68
r 87		99	84
r 88		94	70
r 89		63	20
r 90		95	54

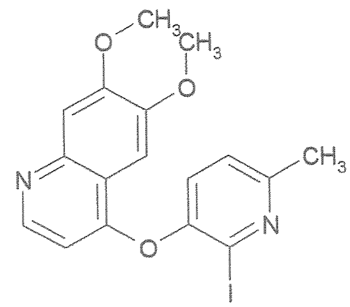
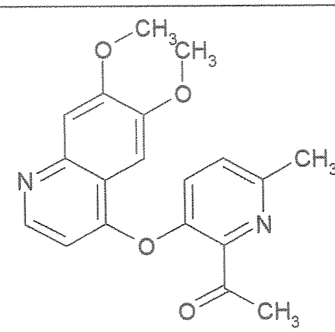
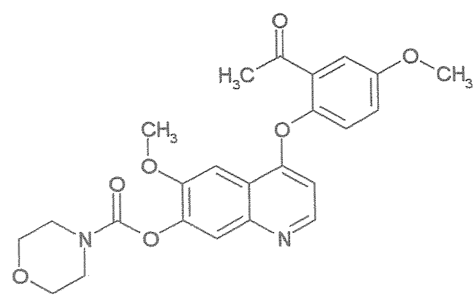
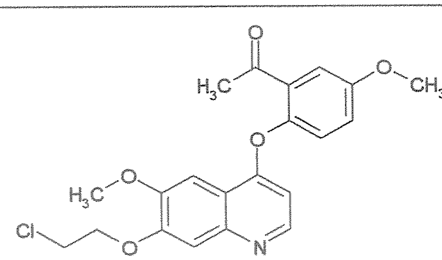
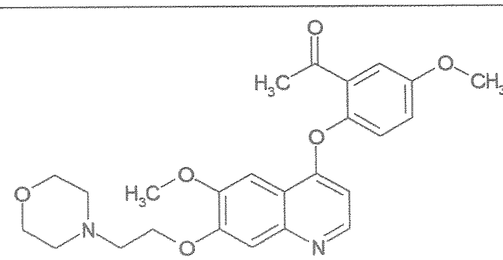
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 91		100	96
r 92		82	25
r 93		88	44
r 94		97	39
r 95		96	67

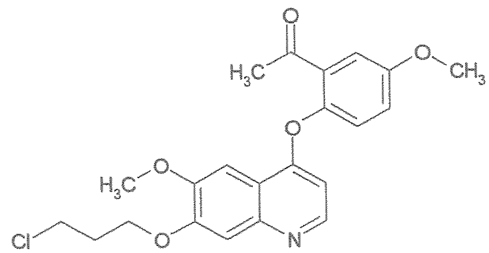
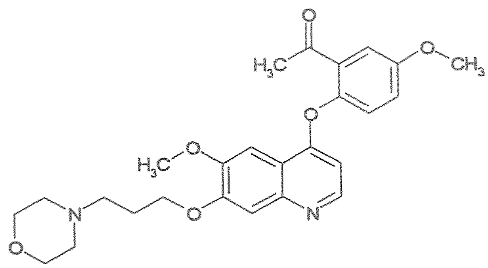
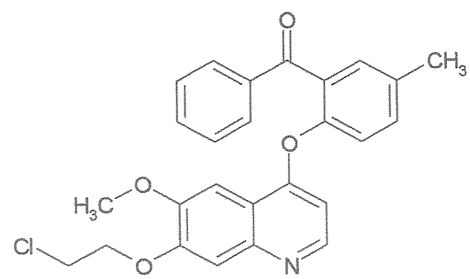
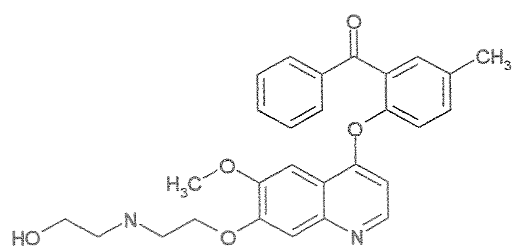
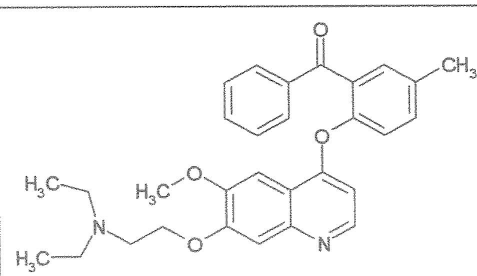
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 96		65	19
r 97		92	14
r 98		93	4
r 99		92	7
r 100		82	0

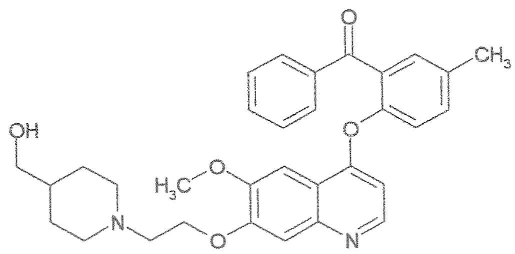
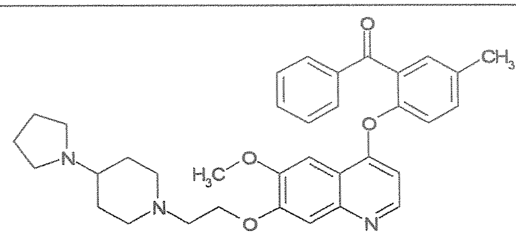
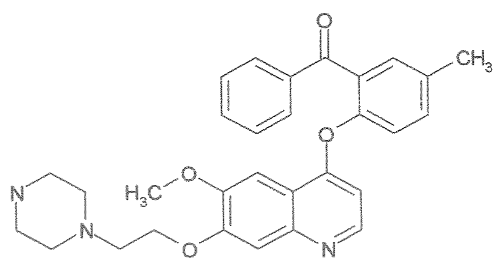
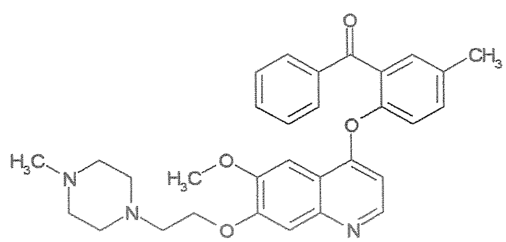
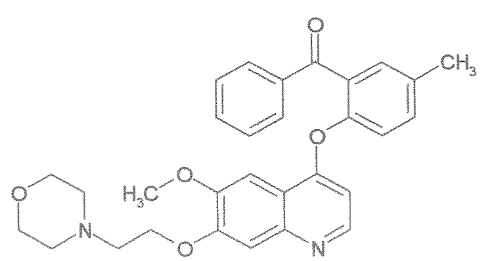
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 101		64	0
r 102		95	33
r 103		84	20
r 104		58	0
r 105		88	17

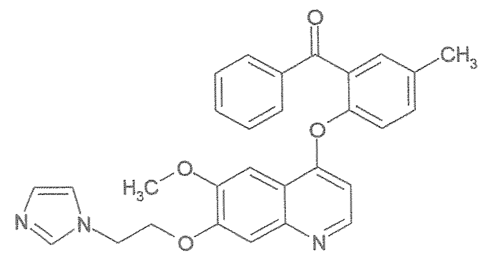
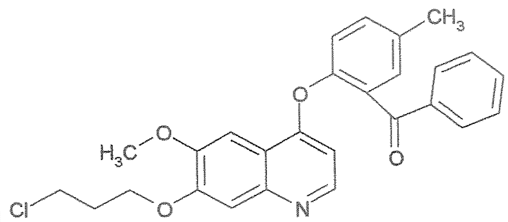
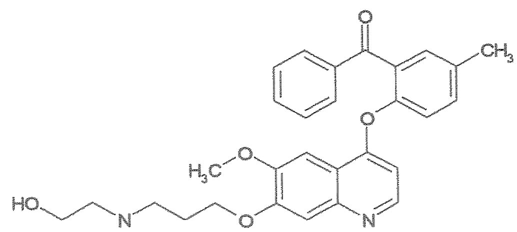
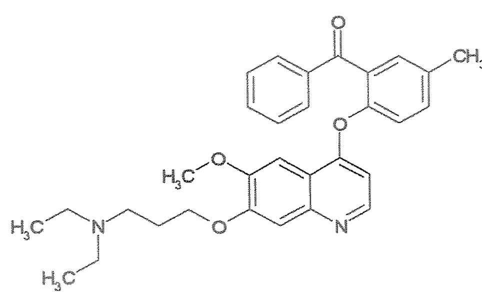
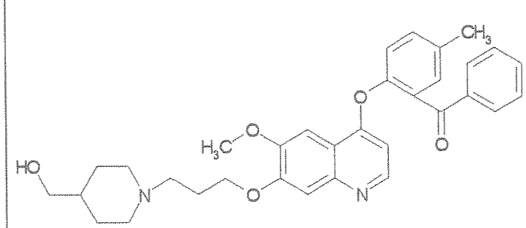
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 106		80	9
r 107		82	0
r 108		73	0
r 109		66	5
r 110		93	55

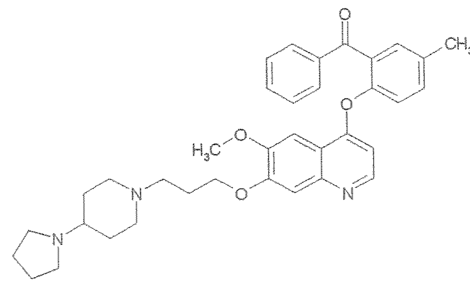
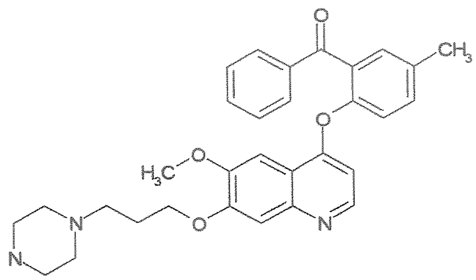
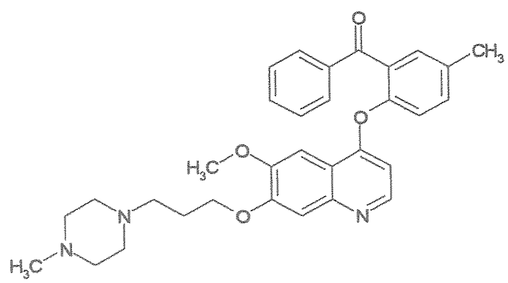
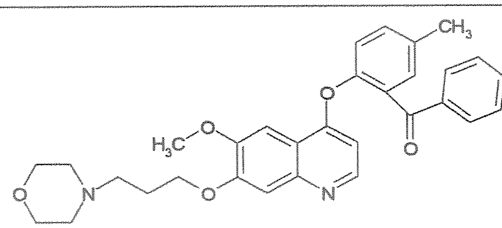
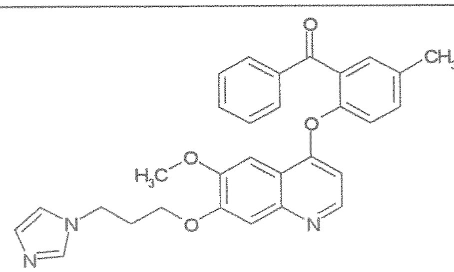
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 111		92	29
r 112		91	44
r 113		96	0
r 114		96	0
r 115		97	74

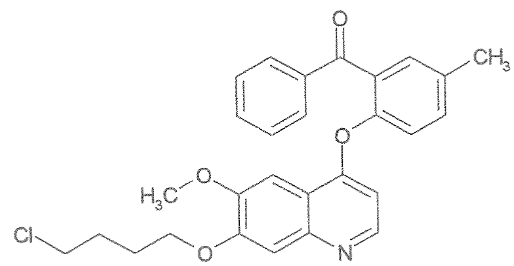
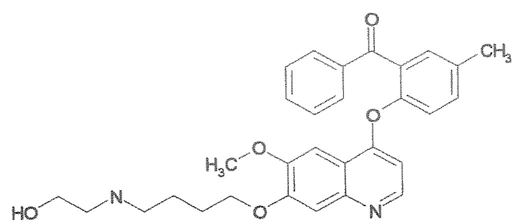
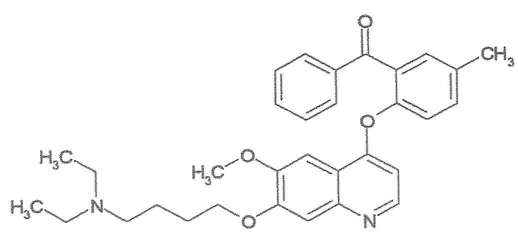
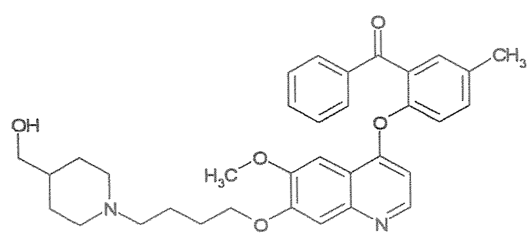
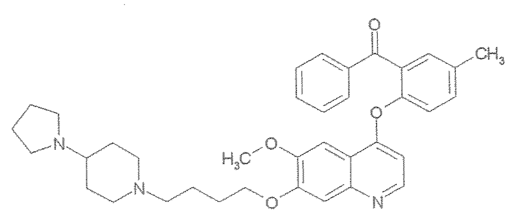
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 116		100	99
r 117		98	84
r 118		100	97
r 119		97	96
r 120		100	94

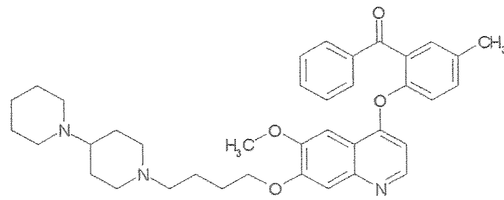
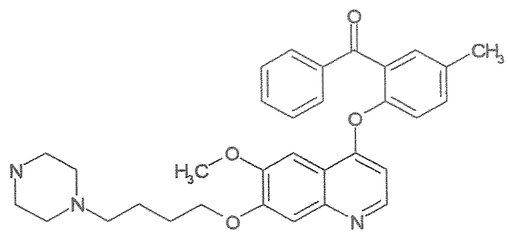
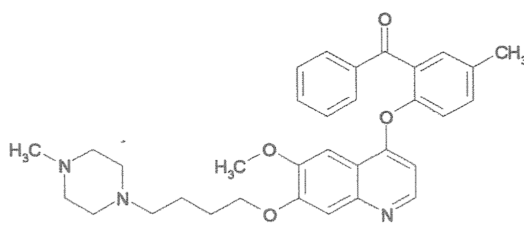
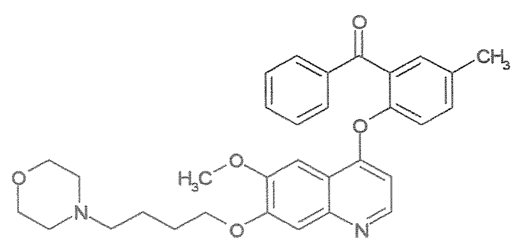
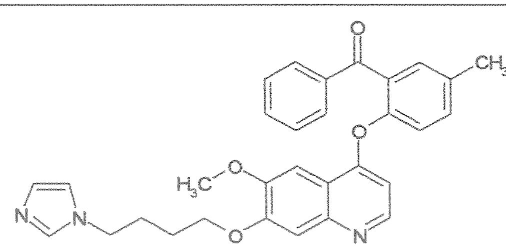
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 121		100	100
r 122		100	100
r 123		100	98
r 124		100	99
r 125		100	98

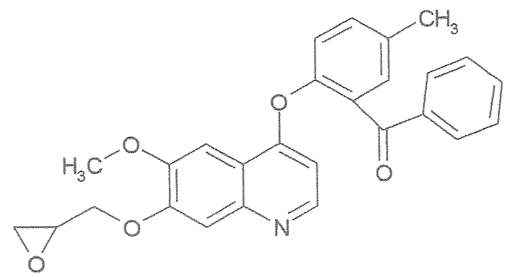
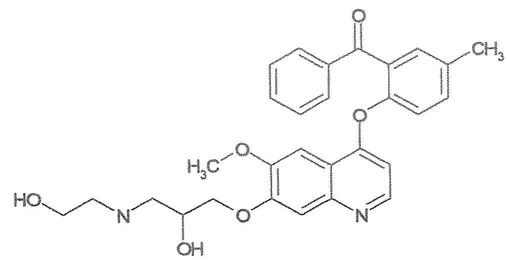
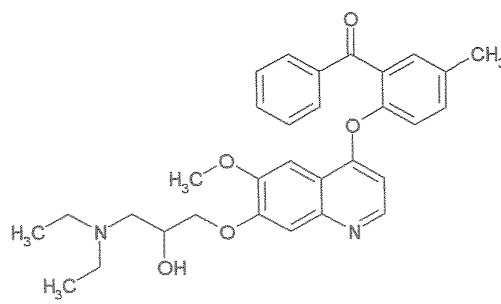
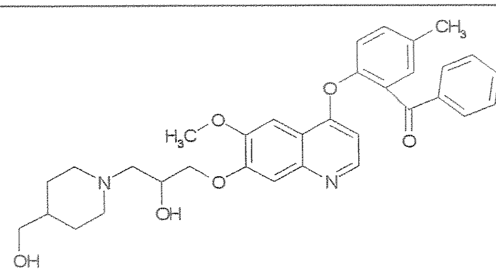
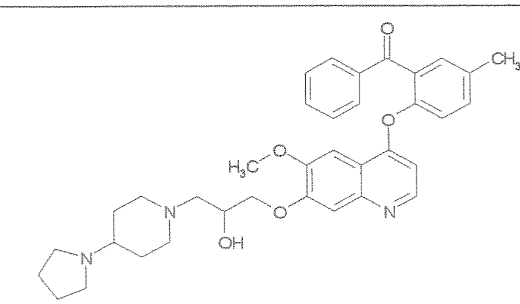
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 126		100	100
r 127		100	99
r 128		100	100
r 129		100	100
r 130		100	90

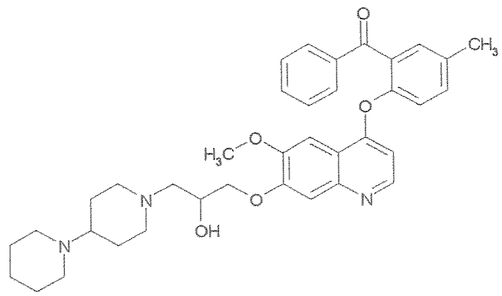
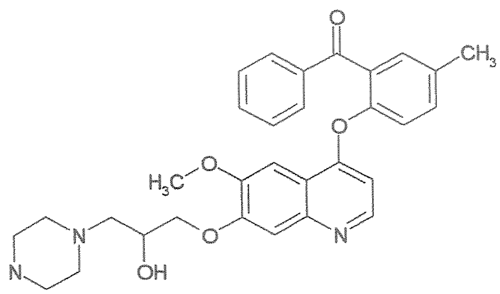
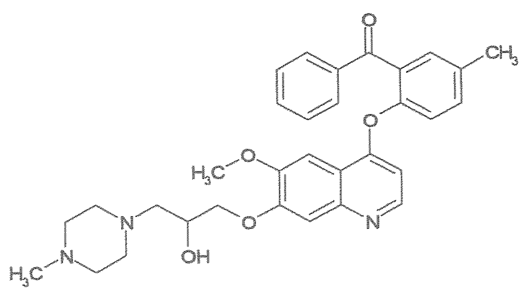
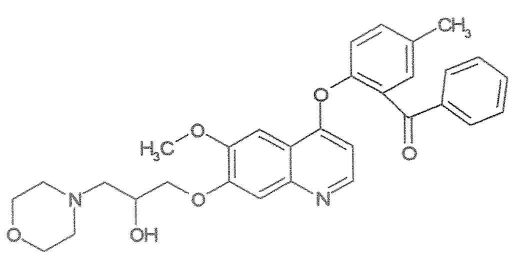
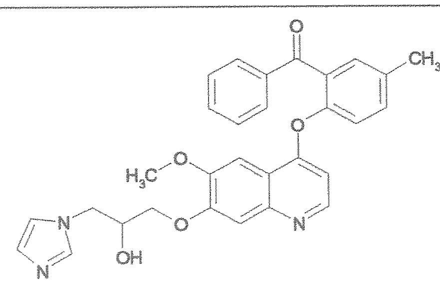
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 131		100	96
r 132		99	72
r 133		100	100
r 134		100	100
r 135		100	100

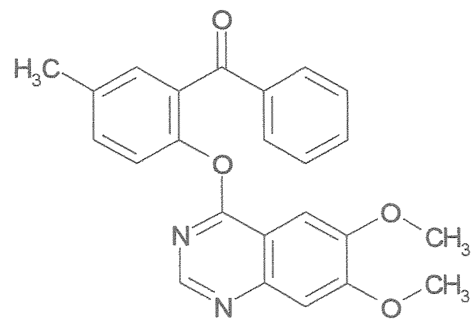
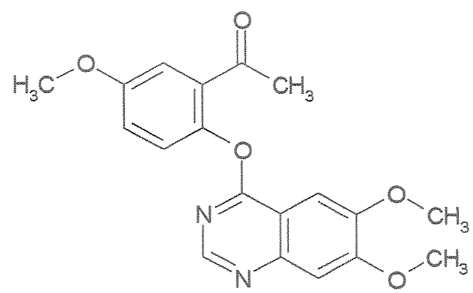
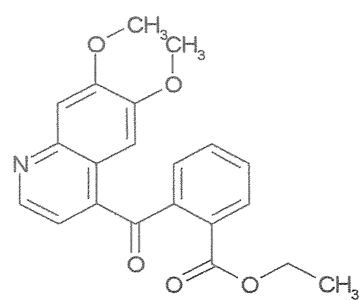
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 136		100	90
r 137		100	100
r 138		100	96
r 139		100	99
r 140		100	85

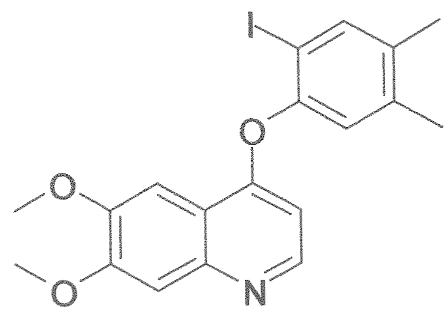
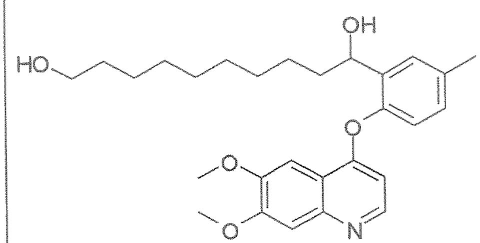
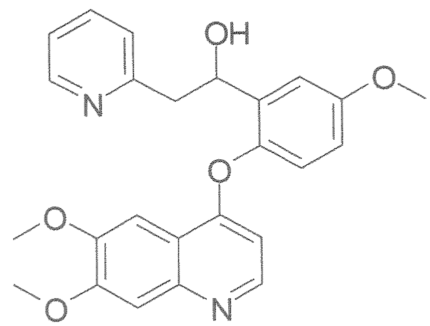
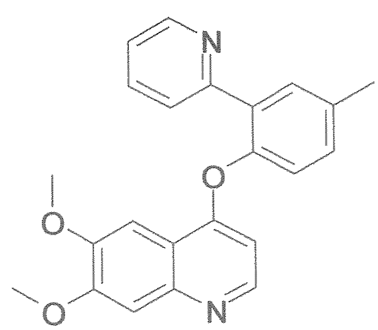
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 141		89	55
r 142		100	100
r 143		100	97
r 144		100	99
r 145		100	87

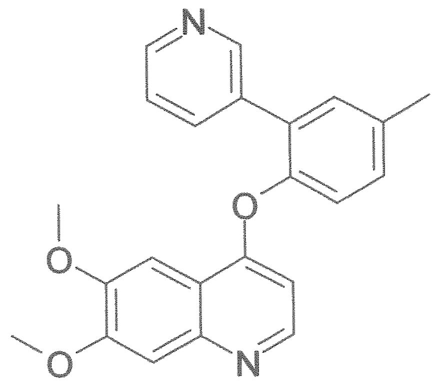
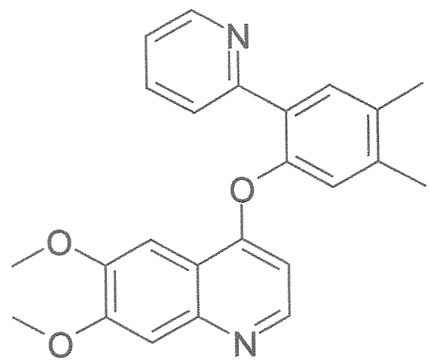
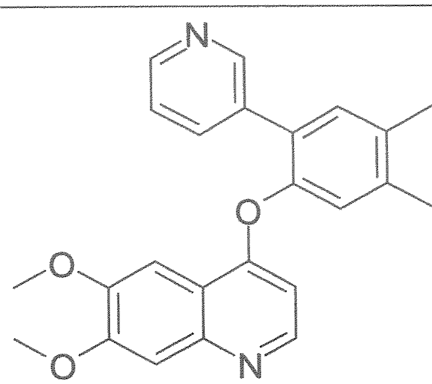
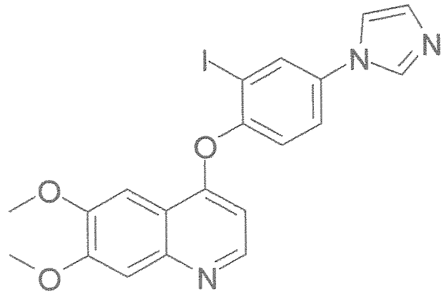
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 146		100	64
r 147		100	98
r 148		100	99
r 149		100	96
r 150		100	97

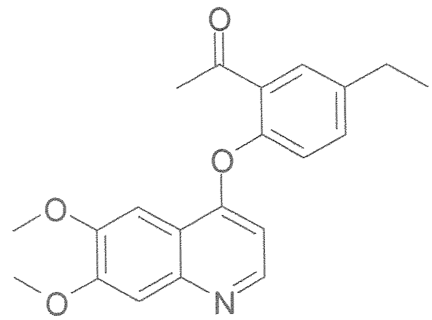
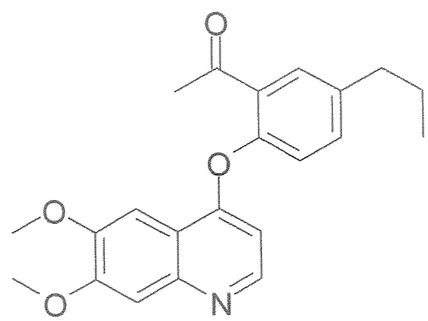
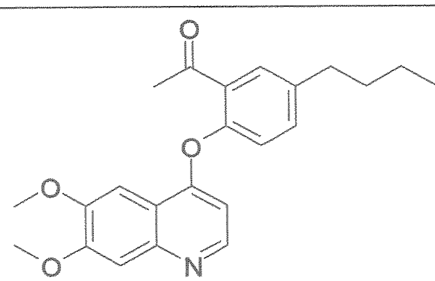
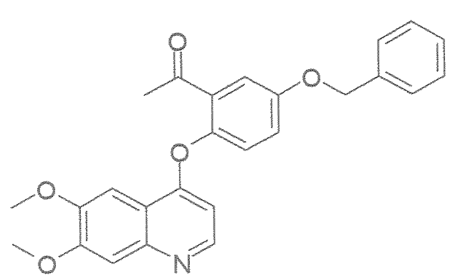
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 151		100	95
r 152		100	99
r 153		100	100
r 154		100	99
r 155		100	100

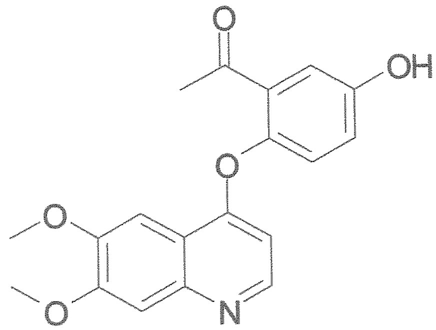
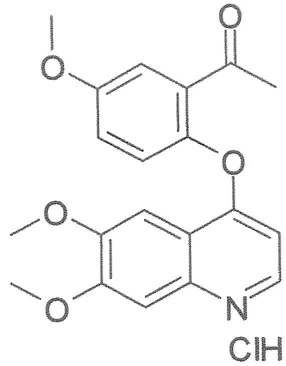
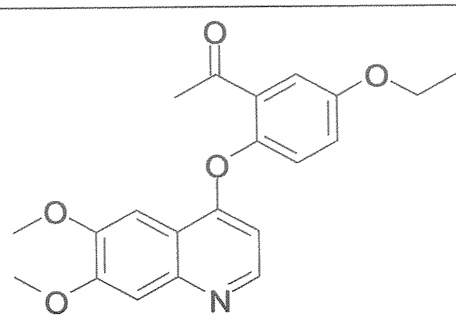
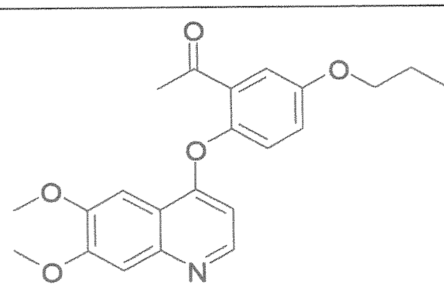
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 156		100	99
r 157		100	100
r 158		100	100
r 159		100	98
r 160		100	98

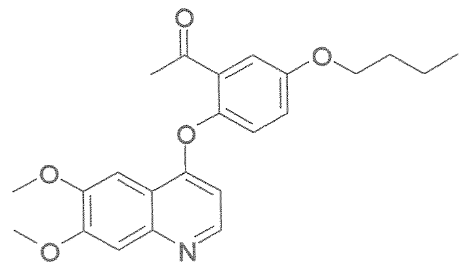
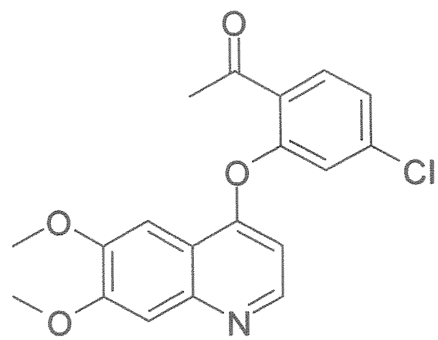
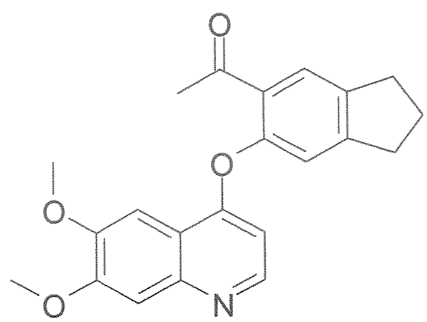
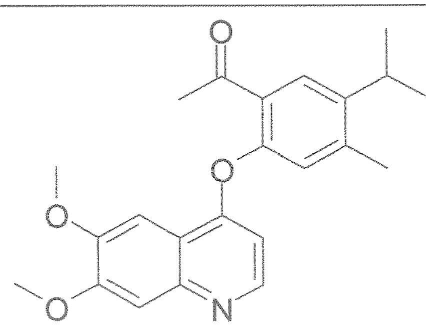
Compound	Molecular structure	TGFβ inhibition rate, %	
		10 μM	3 μM
r 161		83	25
r 162		54	5
r 163		67	3

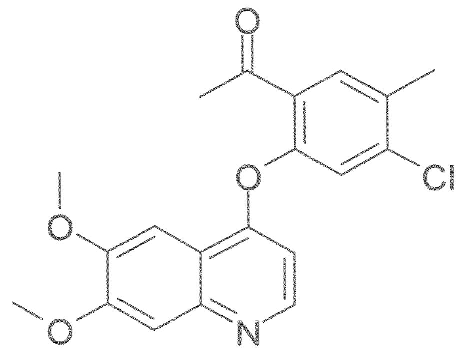
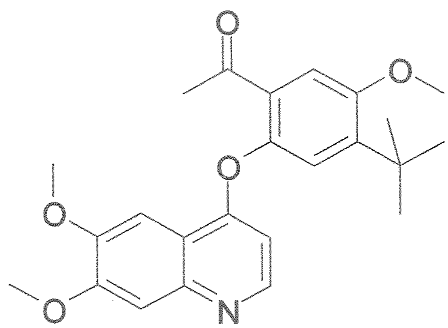
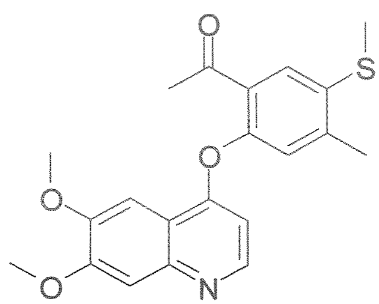
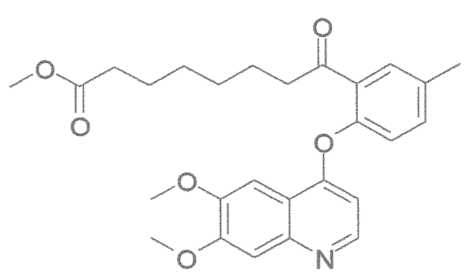
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 164		98	54	
r 165		89	38	
r 166		67	24	
r 167		100	98	

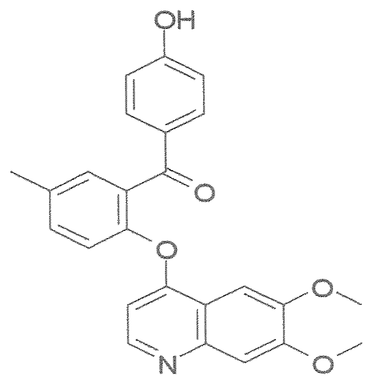
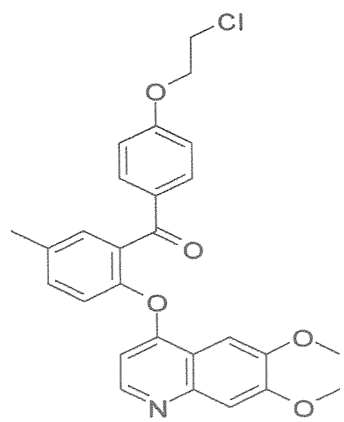
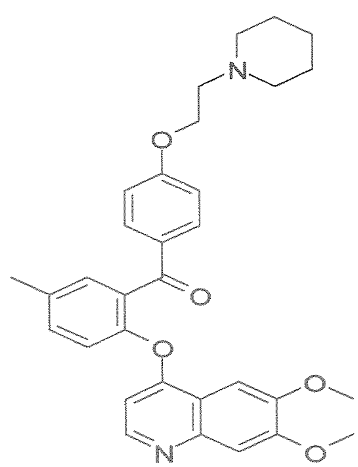
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 168		74	22	
r 169		100	99	
r 170		100	76	
r 171		76	11	

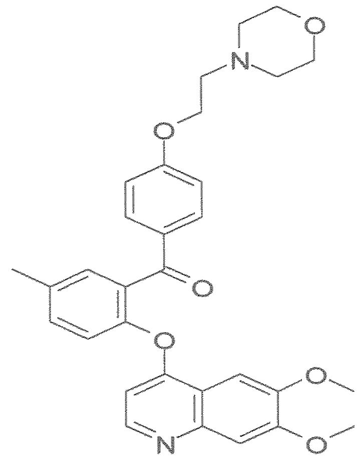
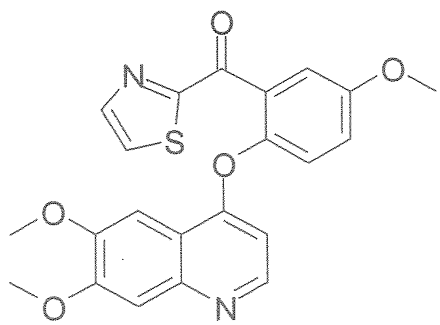
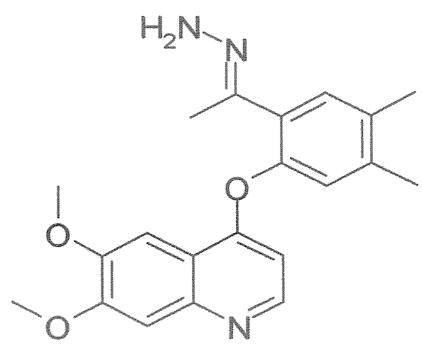
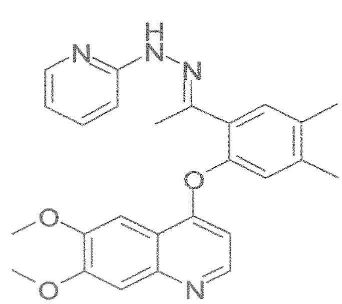
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 172		99	82	
r 173		100	83	
r 174		96	57	
r 175		60	13	

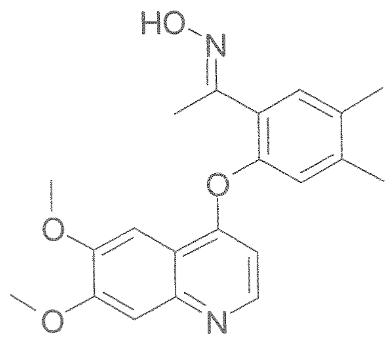
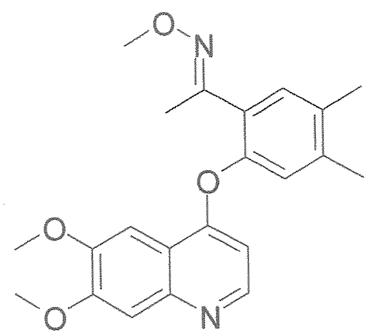
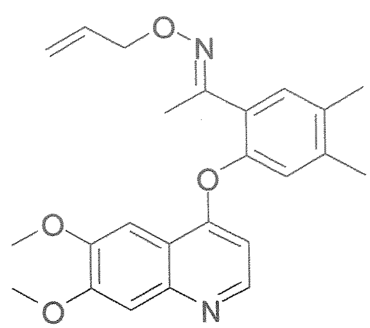
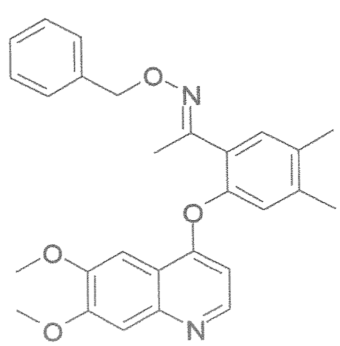
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 176		67	32	
r 177		100	94	
r 178		97	66	
r 179		68	18	

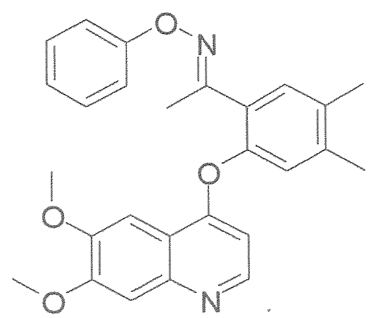
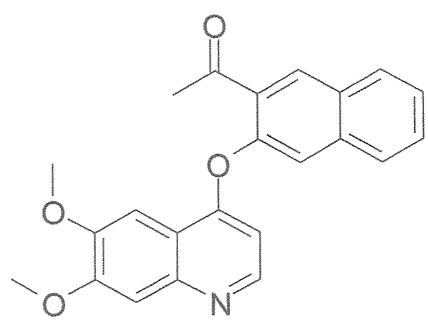
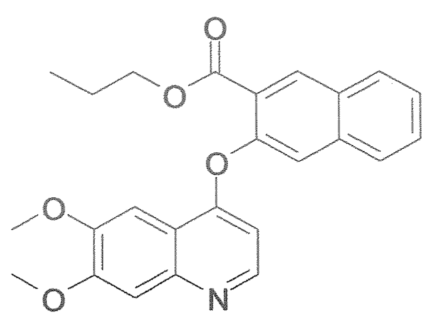
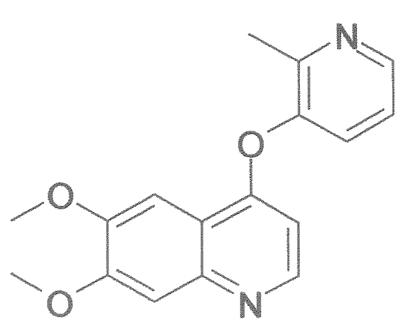
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 180		55	-2	
r 181		82	42	
r 182		96	57	
r 183		100	82	

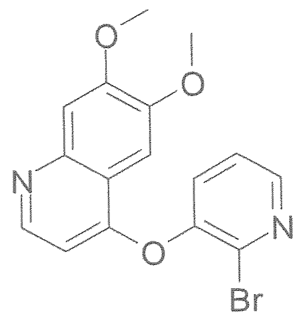
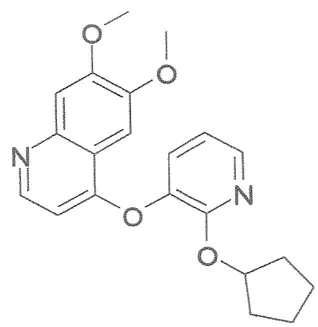
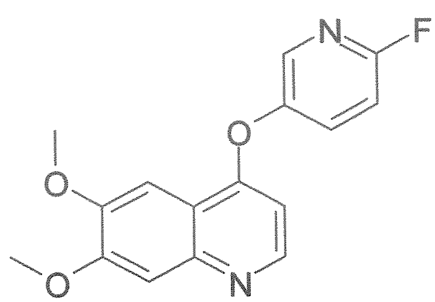
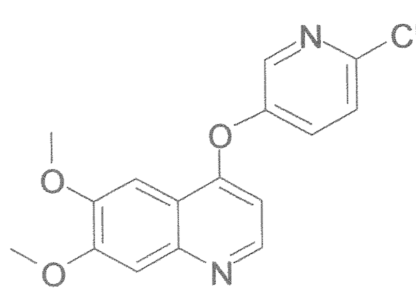
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 184		100	100	
r 185		59	11	
r 186		100	76	
r 187		91	35	

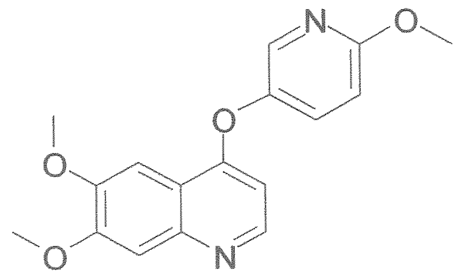
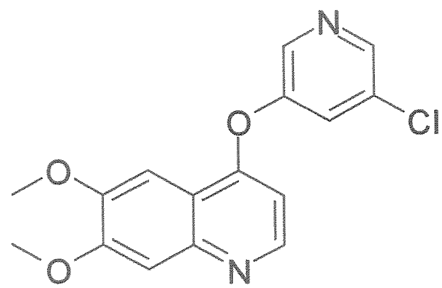
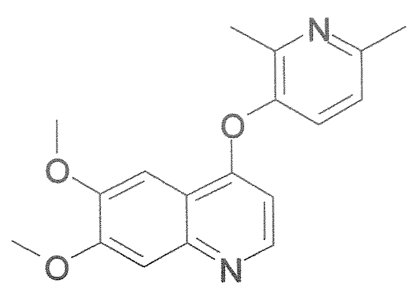
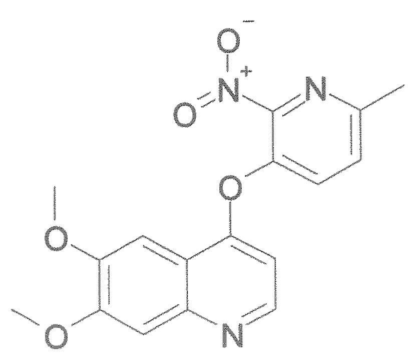
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 188		100	80	
r 189		100	86	
r 190		86	30	

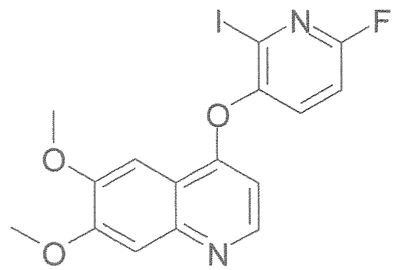
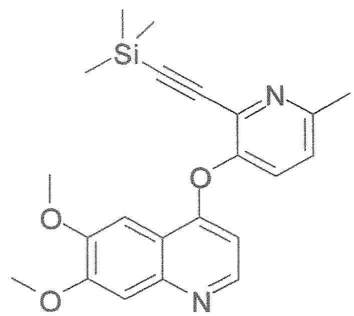
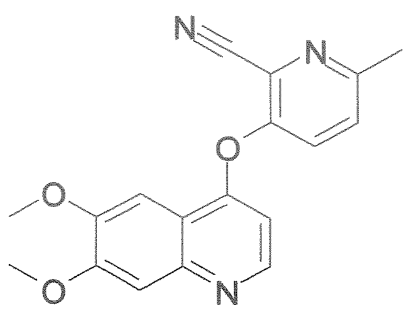
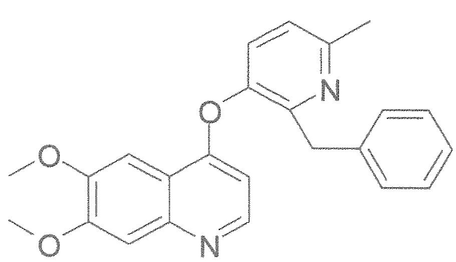
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 191		93	39	
r 192		99	79	
r 193		99	74	
r 194		94	47	

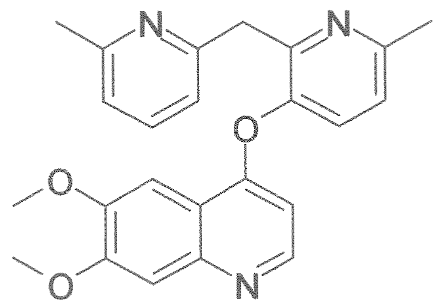
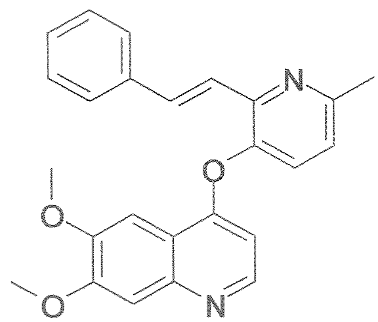
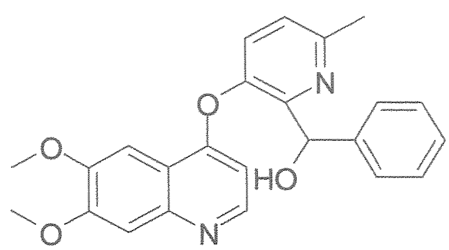
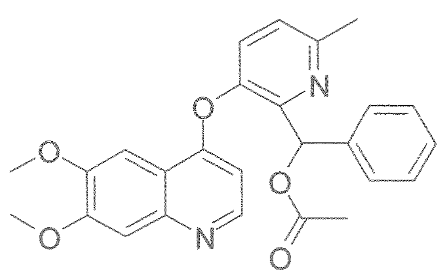
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 195		100	99	
r 196		83	41	
r 197		88	40	
r 198		80	32	

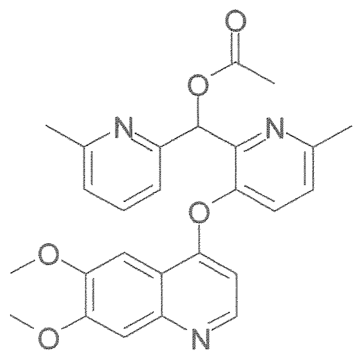
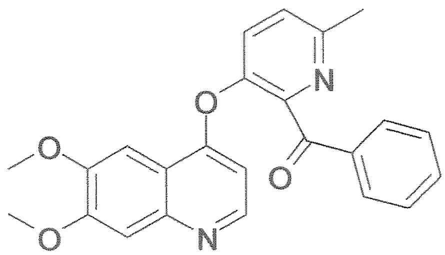
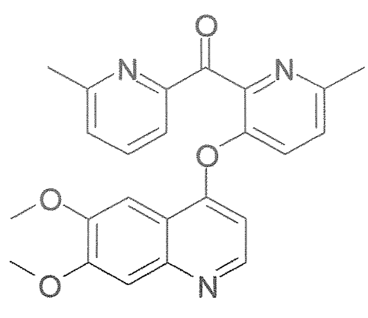
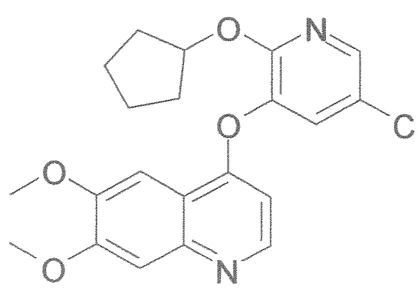
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 199		59	14	
r 200		100	94	
r 201		100	79	
r 202		54	20	

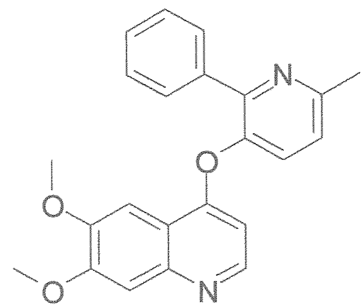
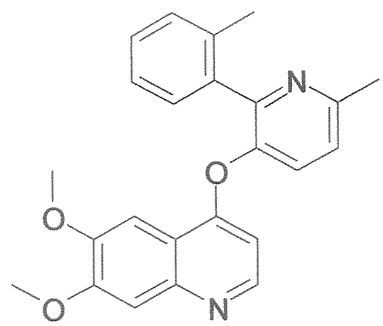
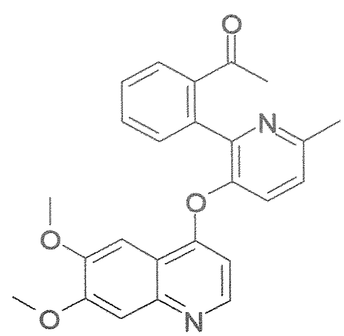
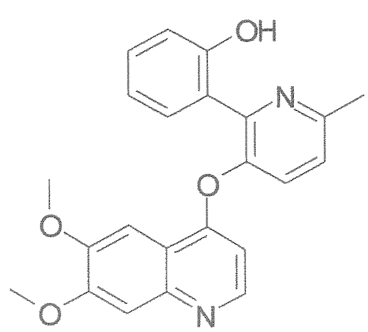
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 203		52	19	
r 204		77	14	
r 205		57	26	
r 206		94	69	

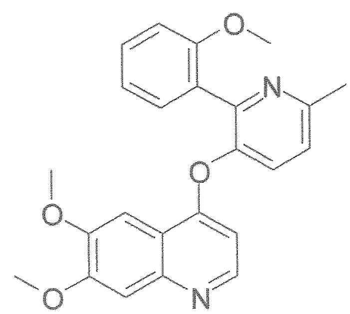
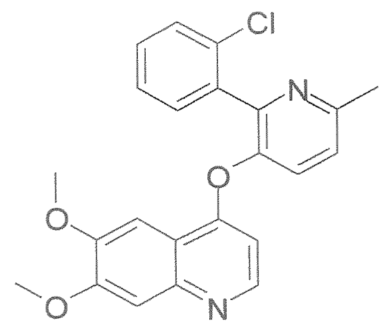
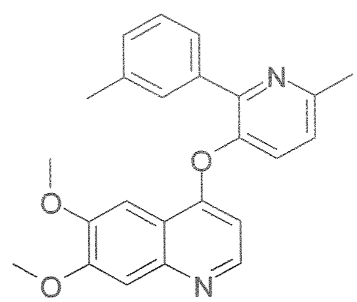
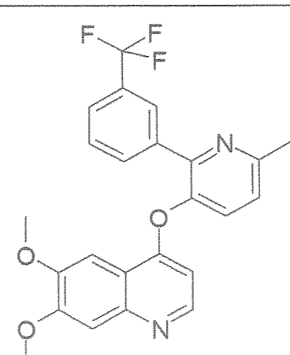
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 207		99	77	
r 208		73	18	
r 209		100	99	
r 210		80	45	

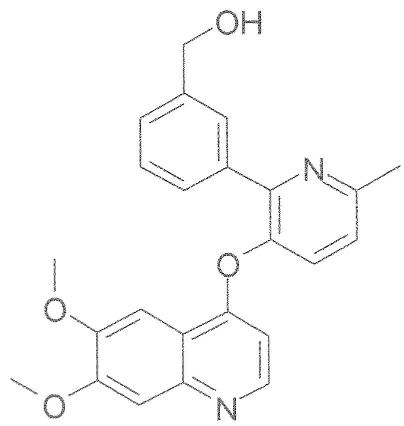
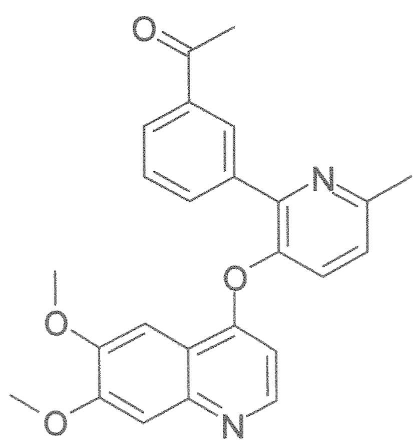
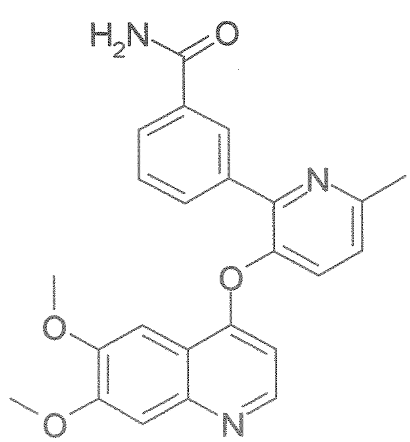
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 211		100	87	
r 212		100	94	
r 213		65	28	
r 214		100	99	

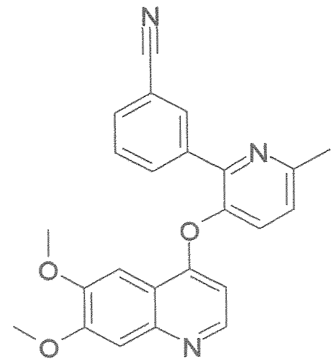
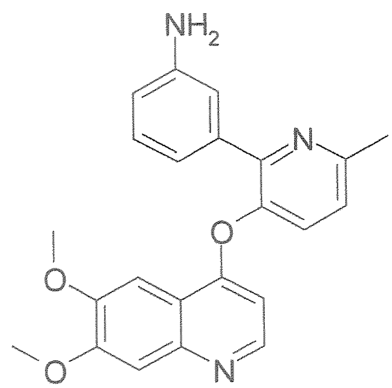
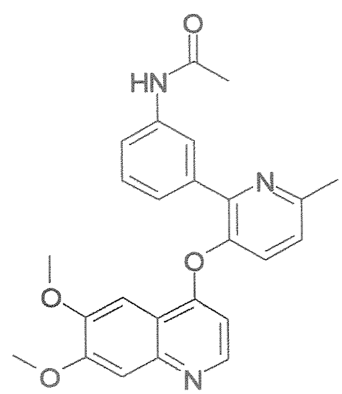
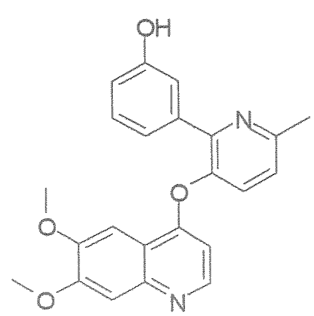
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 215		99	72	
r 216		73	22	
r 217		100	91	
r 218		56	21	

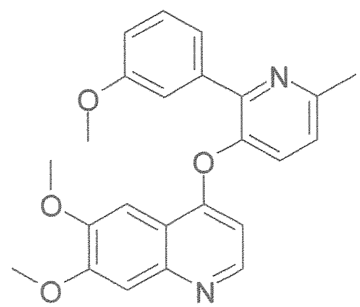
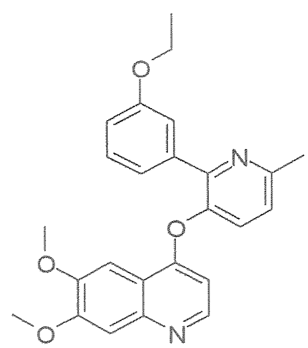
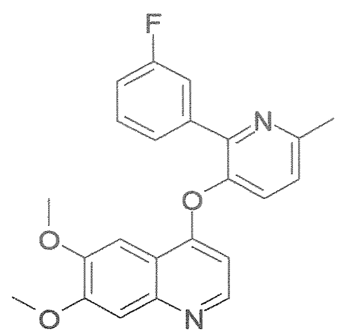
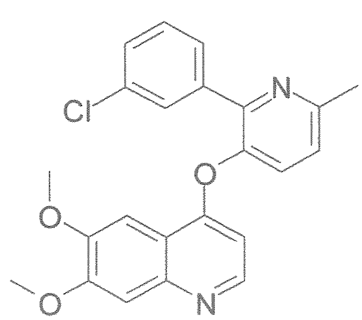
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 219		67	20	
r 220		100	99	
r 221		98	71	
r 222		100	44	

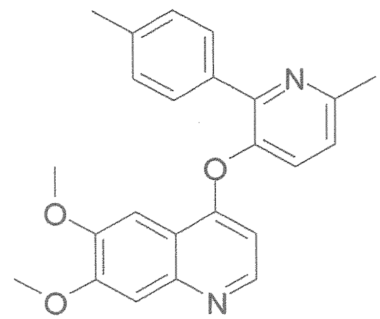
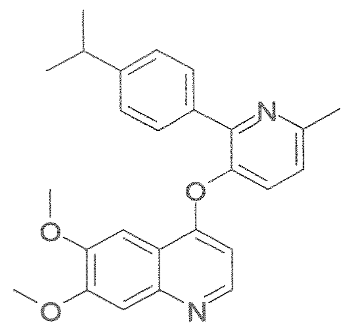
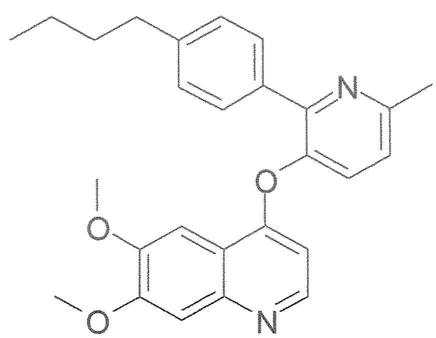
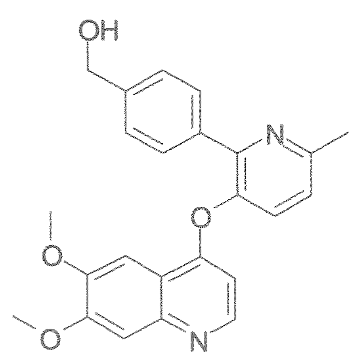
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 223		100	99	
r 224		96	69	
r 225		78	39	
r 226		96	60	

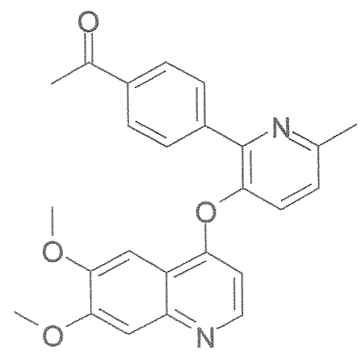
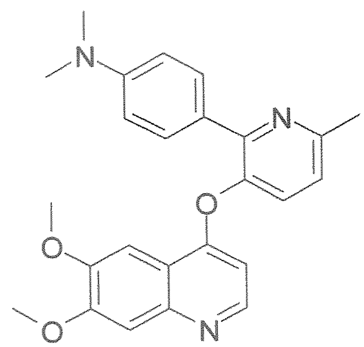
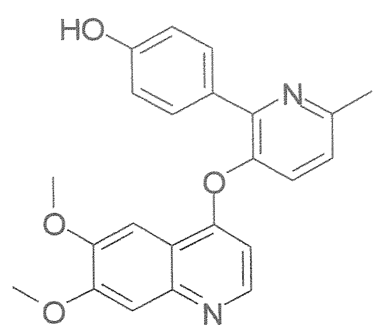
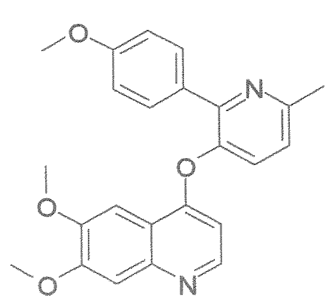
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 227		87	50	
r 228		100	88	
r 229		100	99	
r 230		97	60	

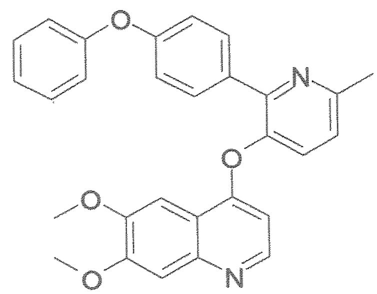
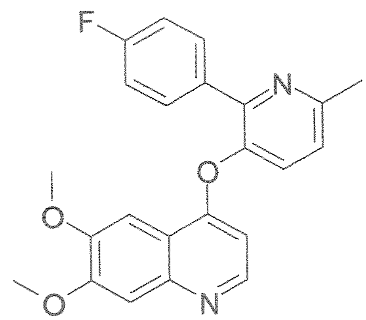
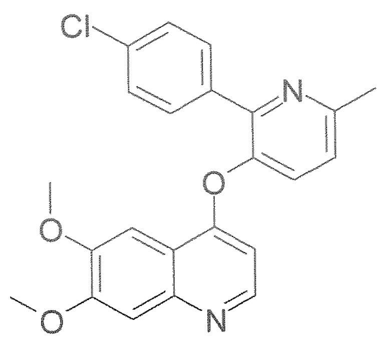
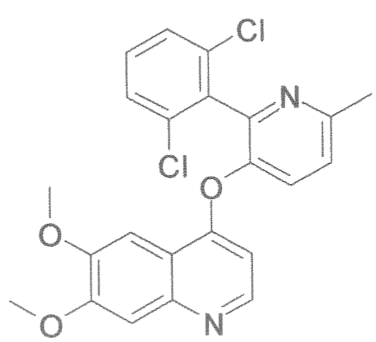
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 231		100	100	
r 232		79	66	
r 233		100	98	

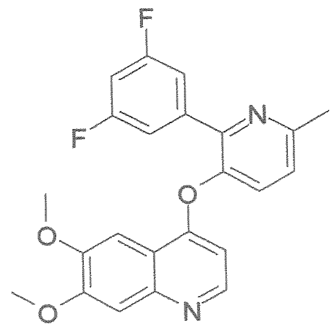
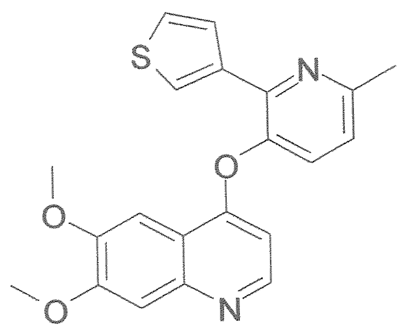
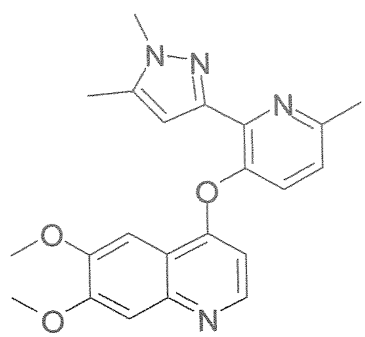
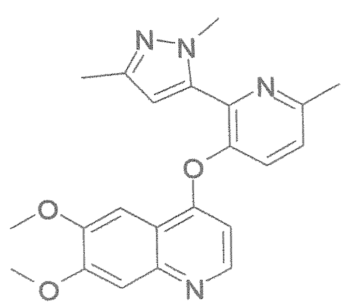
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 234		100	87	
r 235		100	100	
r 236		100	90	
r 237		100	100	

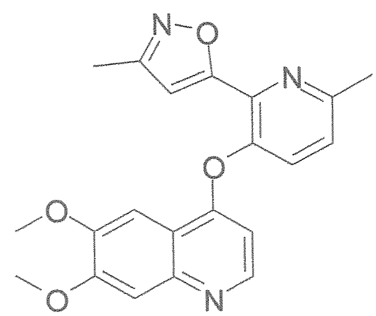
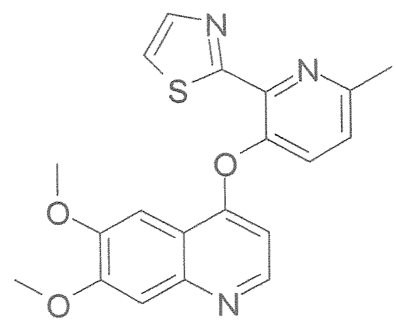
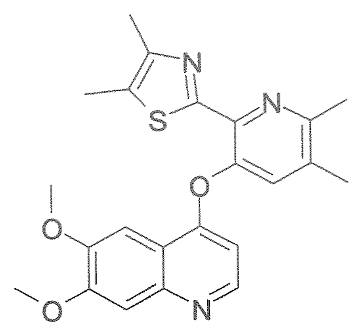
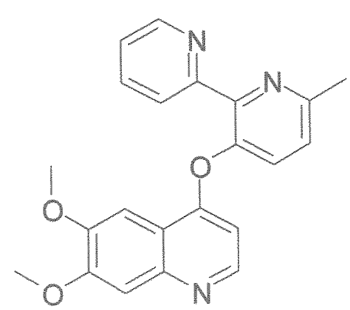
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 238		100	92	
r 239		100	83	
r 240		100	100	
r 241		100	96	

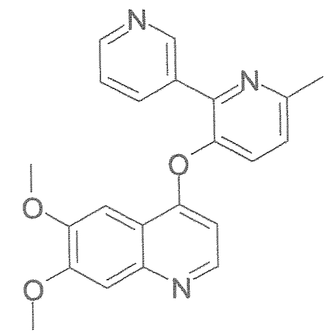
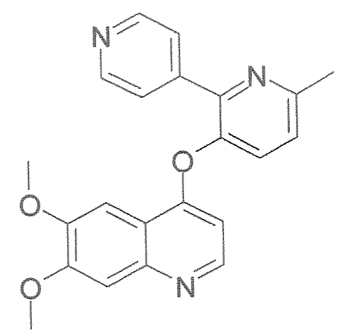
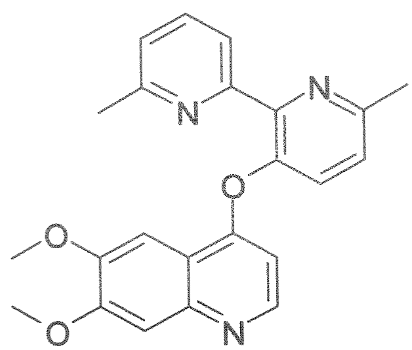
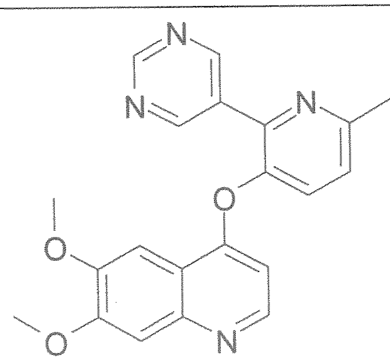
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 242		99	68	
r 243		62	-7	
r 244		63	-3	
r 245		99	80	

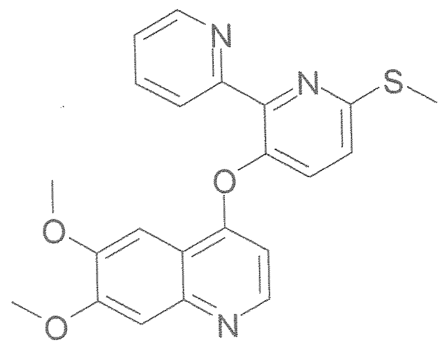
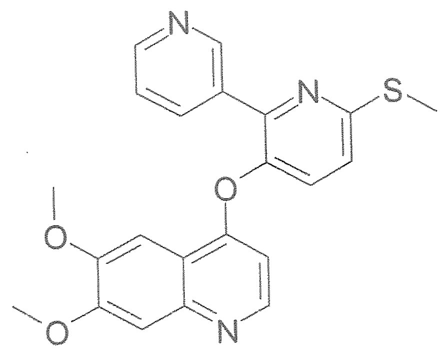
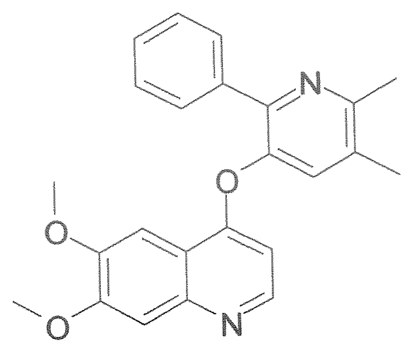
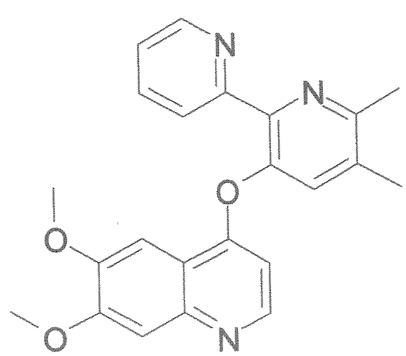
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 246		93	64	
r 247		100	93	
r 248		100	99	
r 249		98	52	

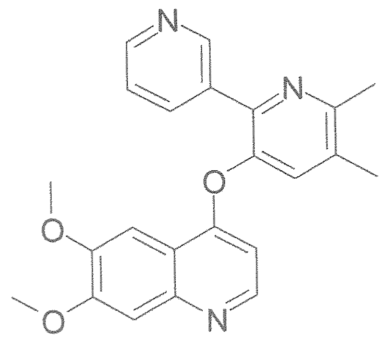
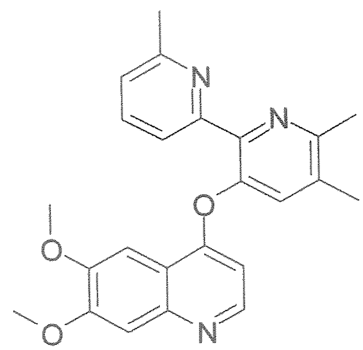
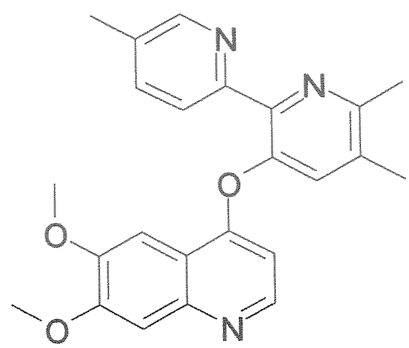
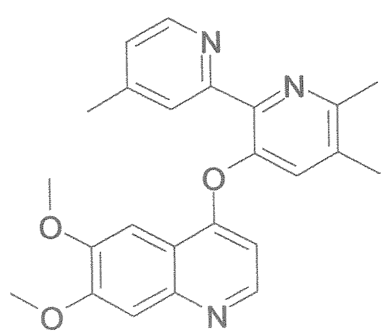
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 250		81	34	
r 251		100	84	
r 252		78	16	
r 253		97	68	

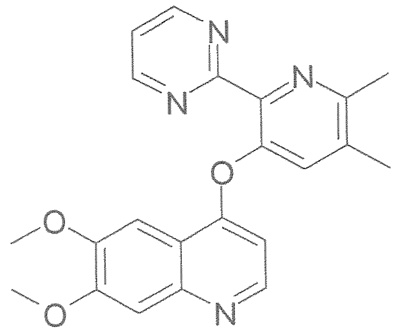
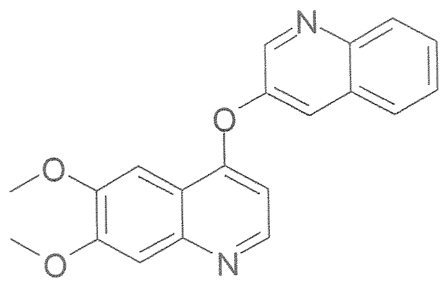
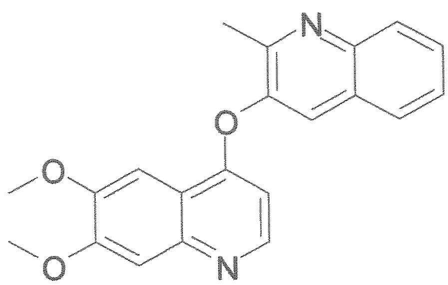
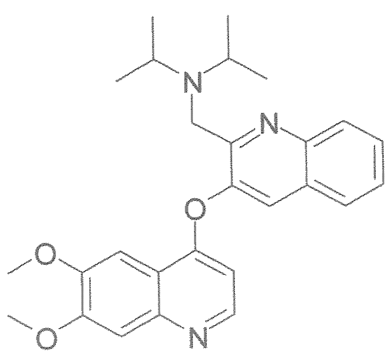
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 254		100	100	
r 255		100	93	
r 256		100	98	
r 257		62	15	

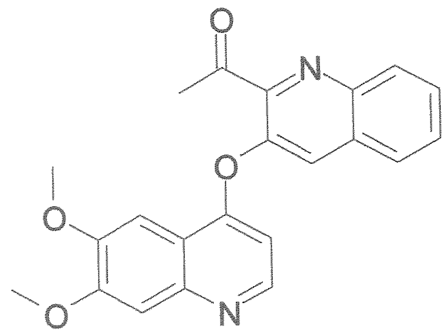
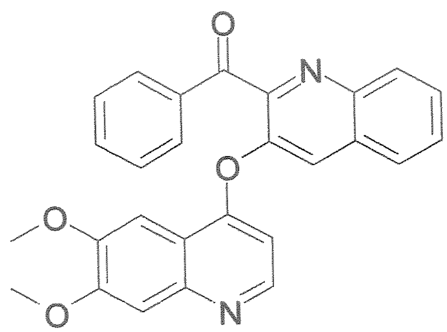
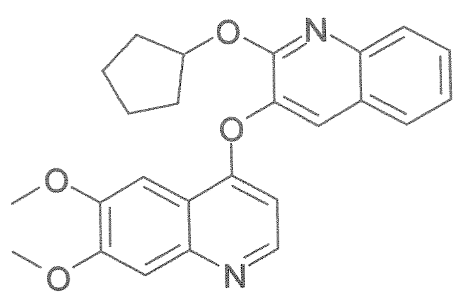
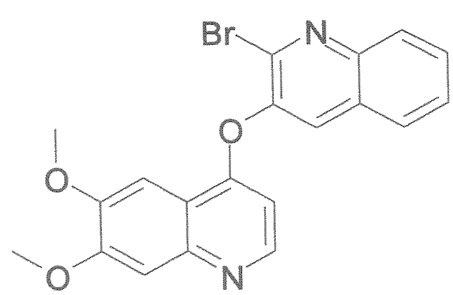
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 258		100	99	
r 259				100
r 260		100	96	
r 261		100	100	

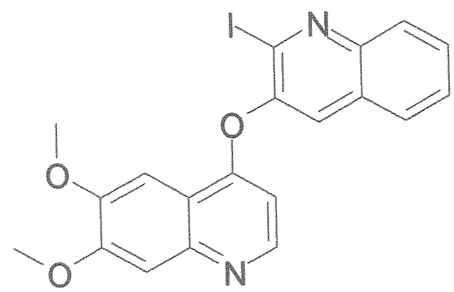
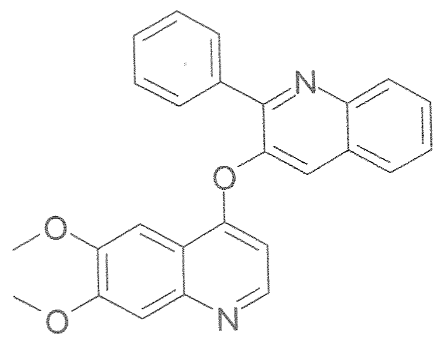
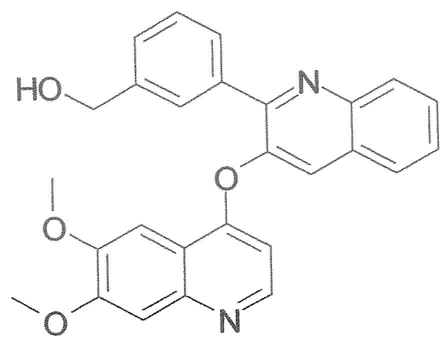
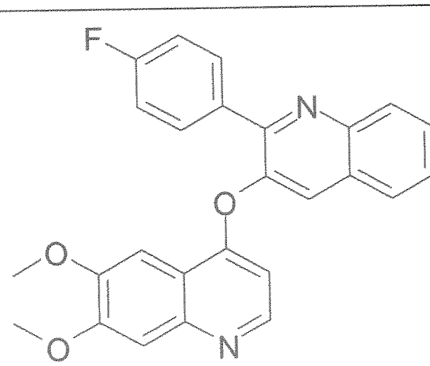
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 262		100	91	
r 263		99	82	
r 264		100	88	
r 265		85	45	

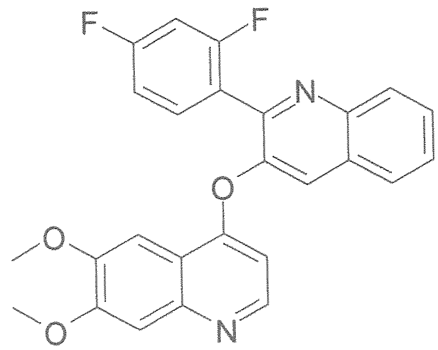
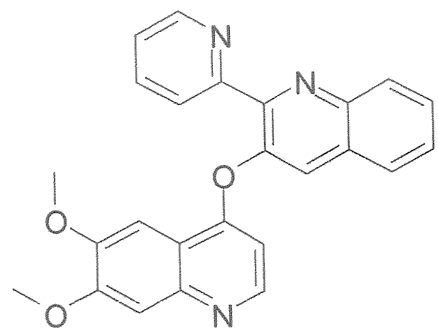
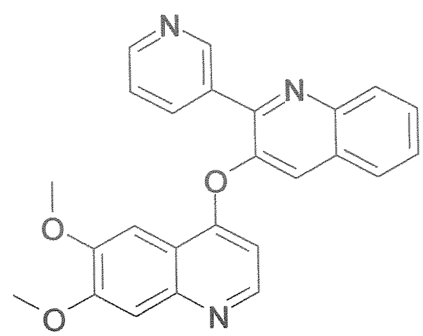
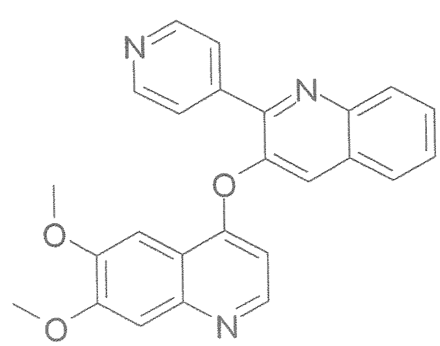
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 266		100	92	
r 267		83	34	
r 268		100	100	
r 269				97

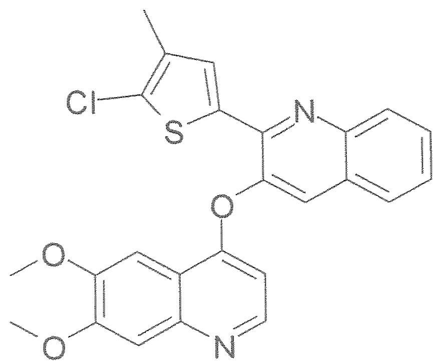
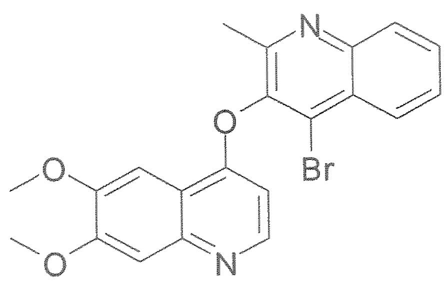
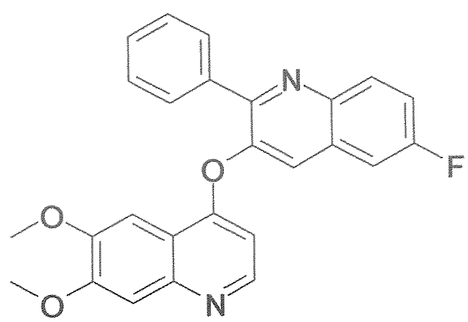
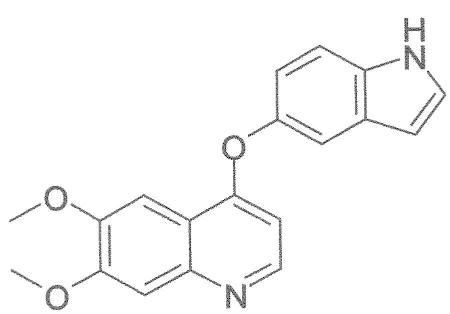
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 270			100	
r 271		100	94	
r 272		100	98	
r 273		100	99	

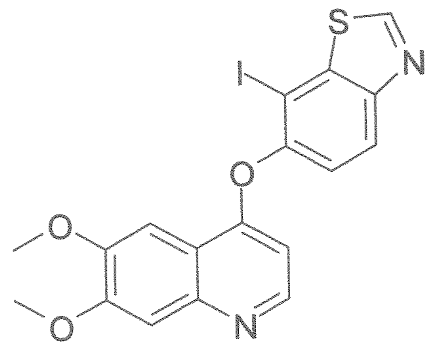
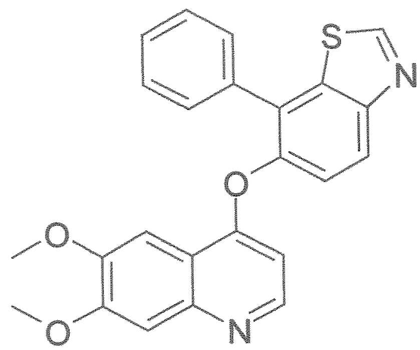
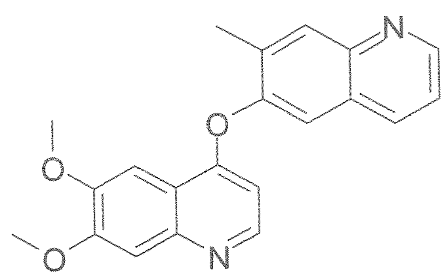
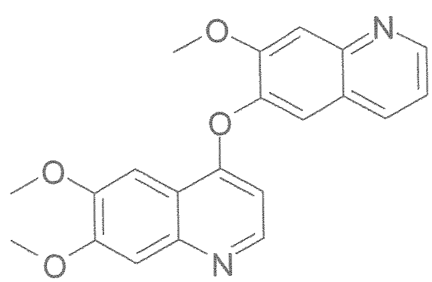
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 274			97	
r 275		90	45	
r 276		100	89	
r 277		89	32	

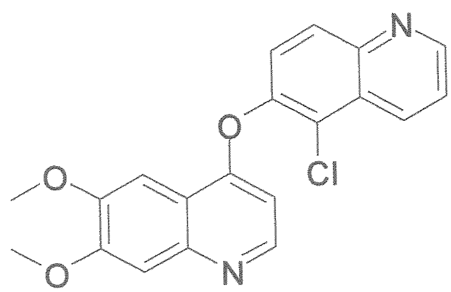
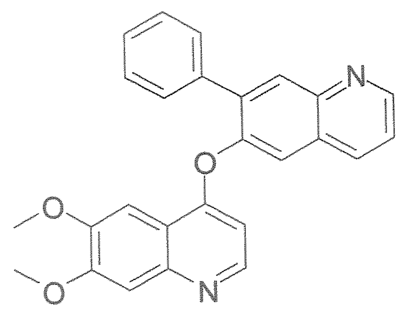
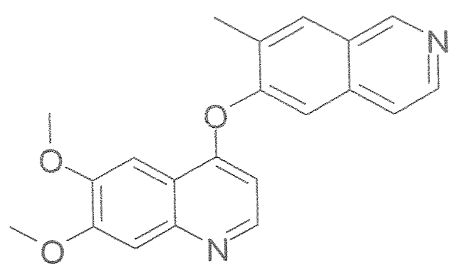
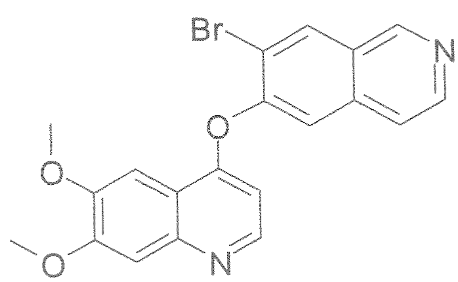
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 278		99	90	
r 279		100	98	
r 280		88	45	
r 281		100	88	

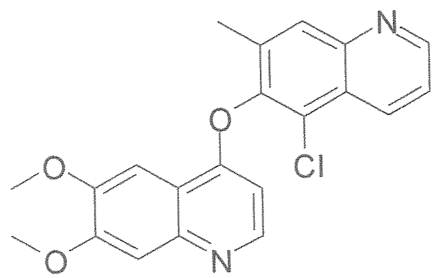
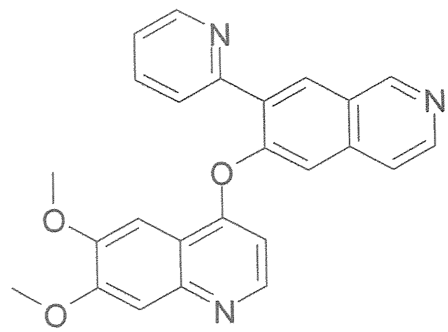
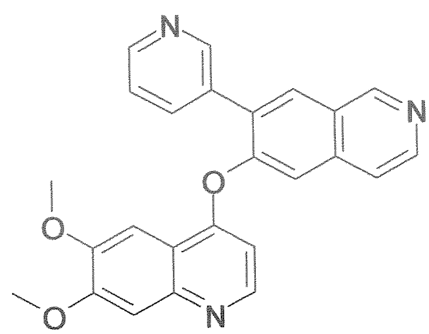
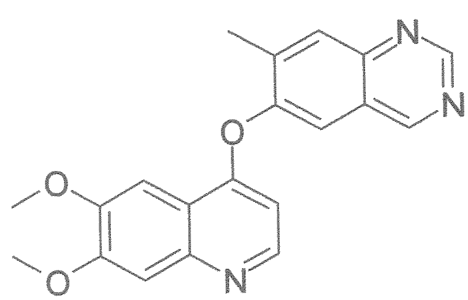
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 282		100	96	
r 283		100	99	
r 284		100	96	
r 285		100	65	

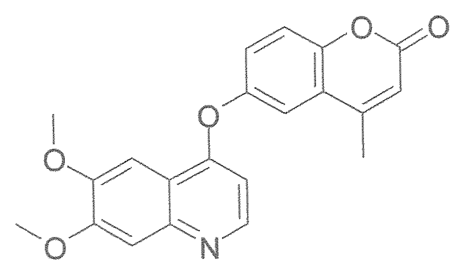
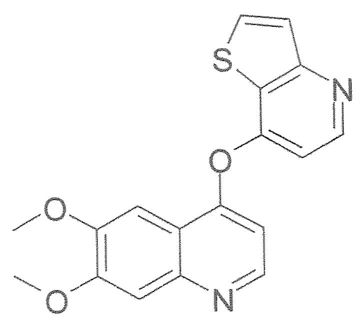
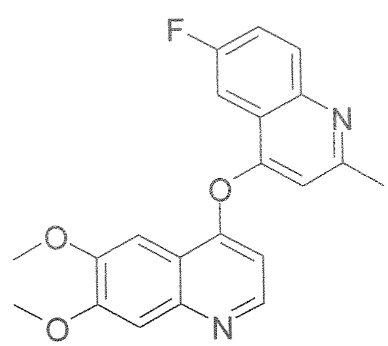
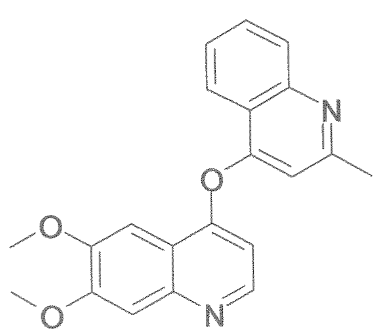
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 286		100	93	
r 287		100	100	
r 288		100	94	
r 289		99	80	

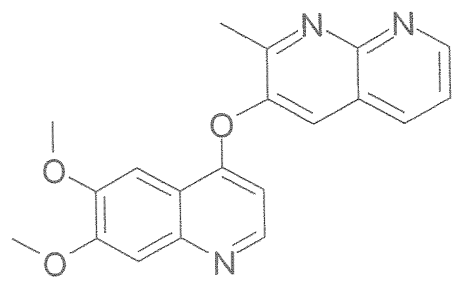
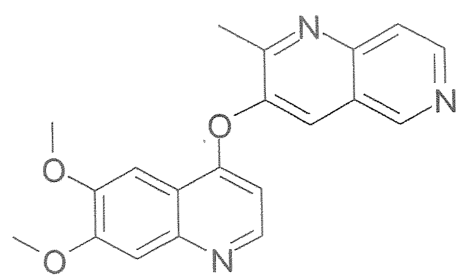
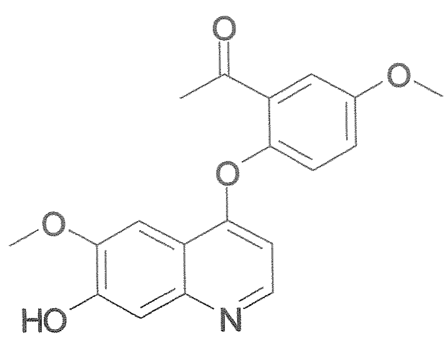
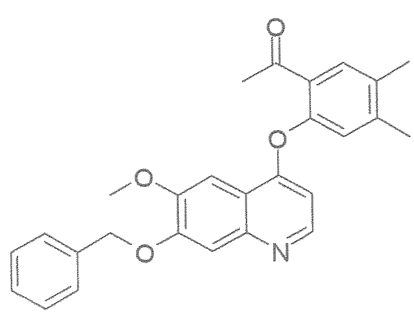
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 290		57	18	
r 291		78	14	
r 292		100	86	
r 293		95	65	

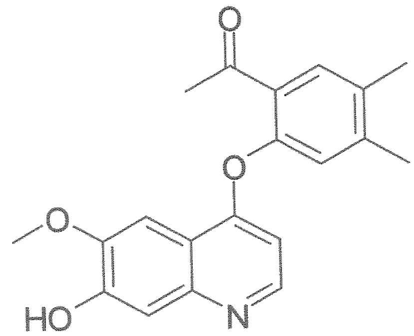
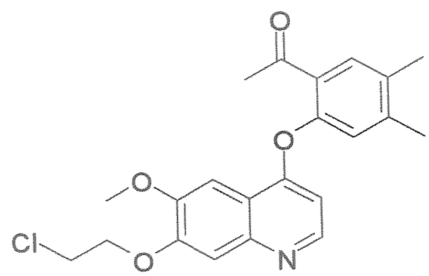
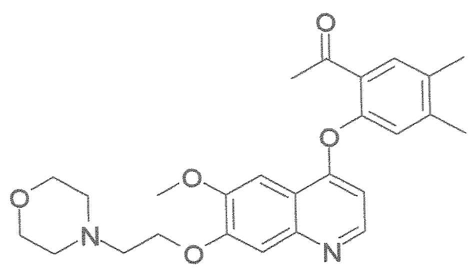
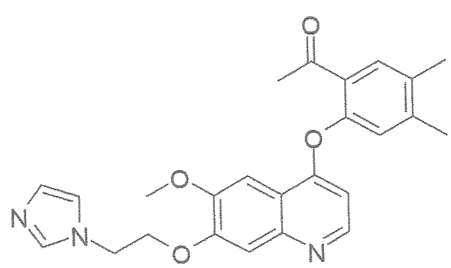
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 294		77	53	
r 295		96	47	
r 296		100	86	
r 297		94	61	

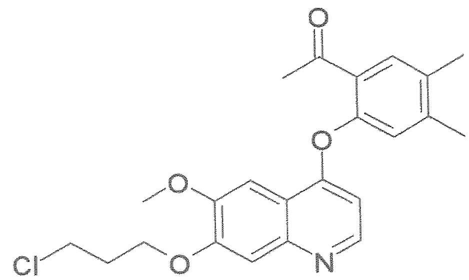
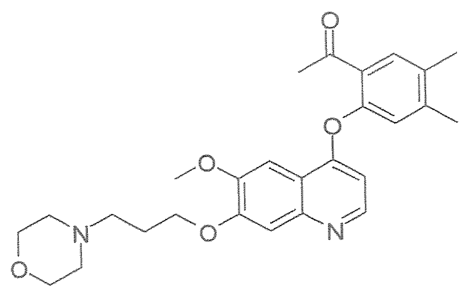
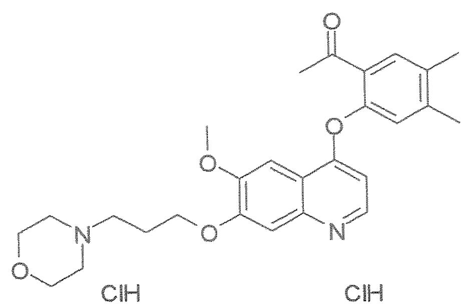
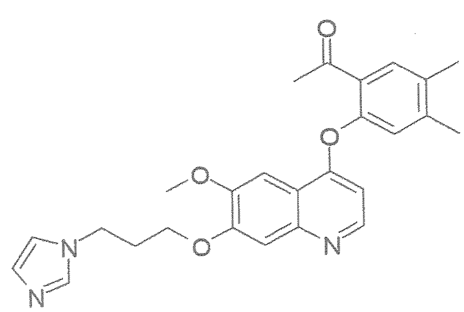
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 298		75	30	
r 299		100	99	
r 300		63	9	
r 301		75	20	

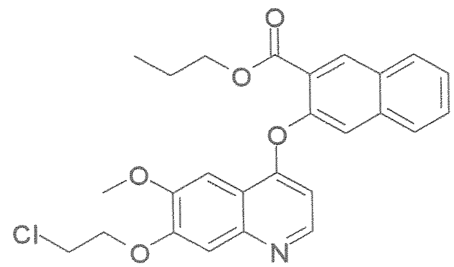
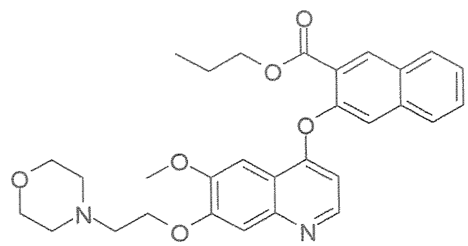
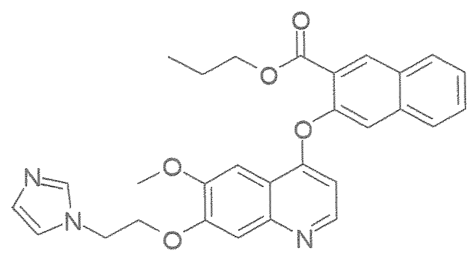
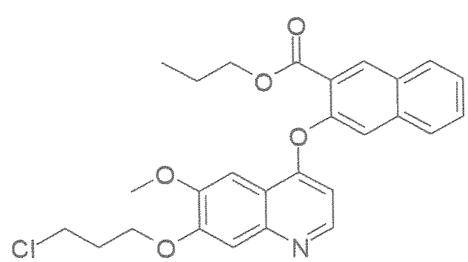
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 302		90	30	
r 303			96	
r 304		64	26	
r 305		64	28	

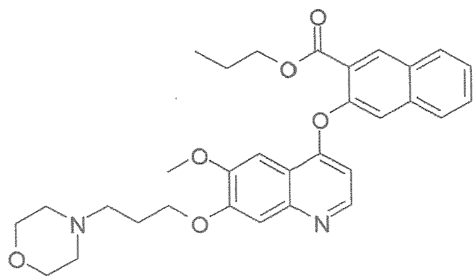
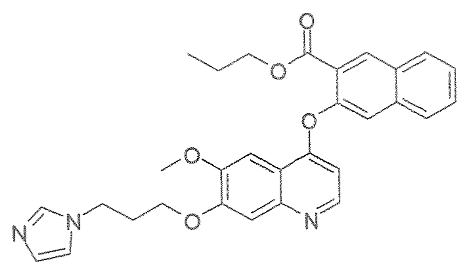
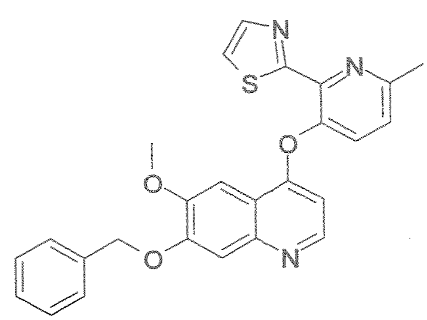
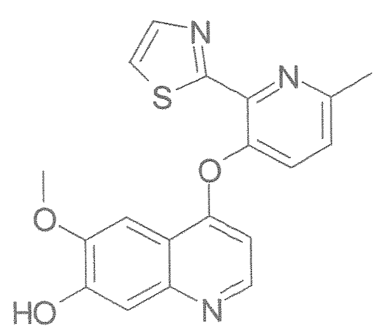
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 306		53	20	
r 307		69	26	
r 308		56	21	
r 309		79	41	

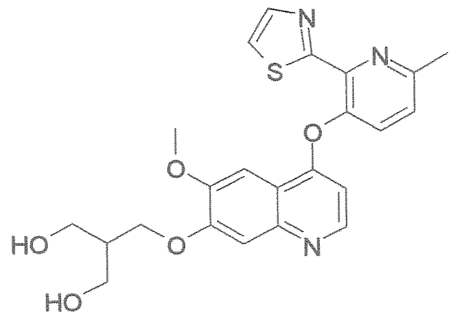
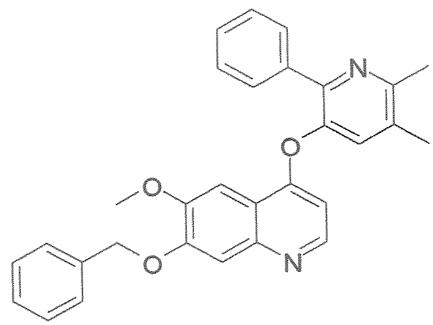
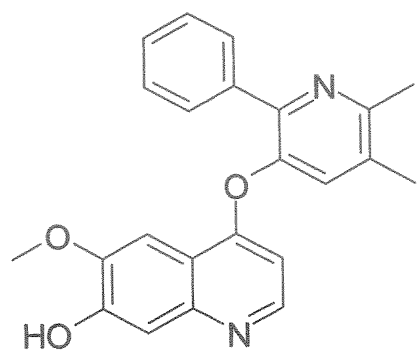
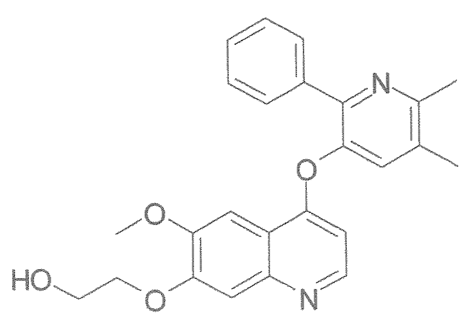
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 310		97	72	
r 311		90	53	
r 312		76	50	
r 313		94	56	

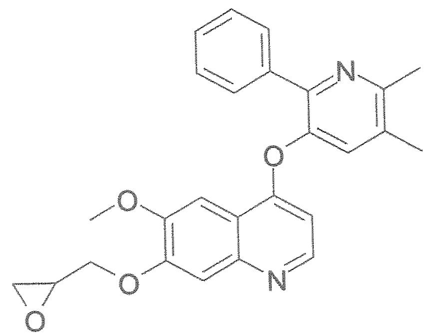
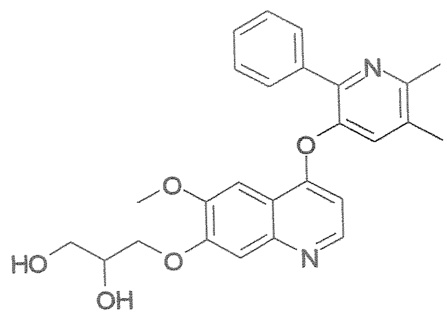
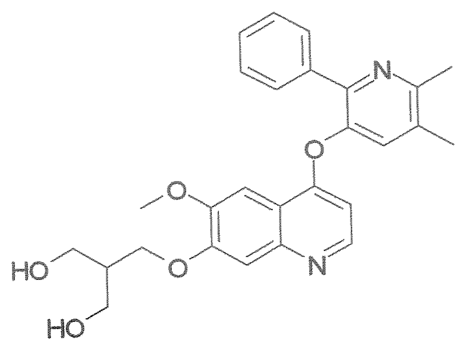
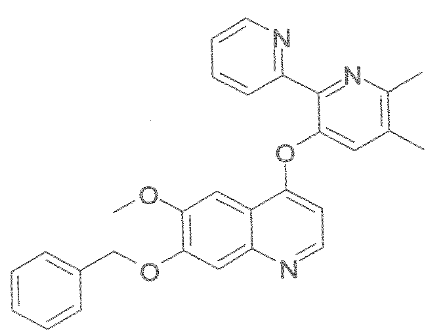
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 314		89	50	
r 315		100	98	
r 316		100	99	
r 317		100	100	

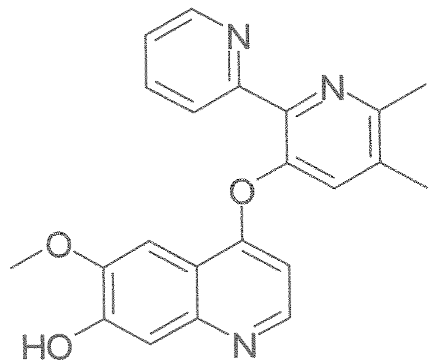
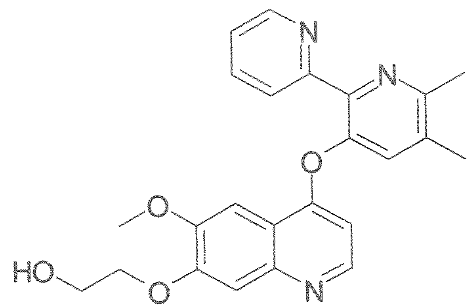
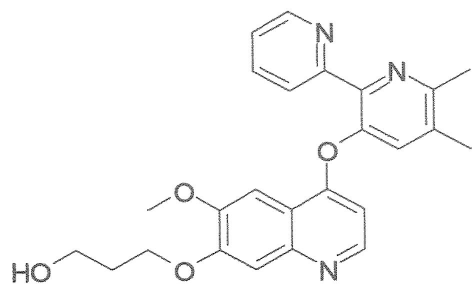
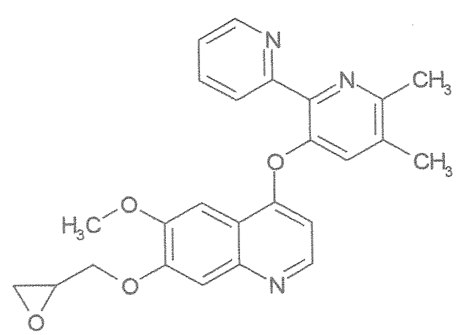
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 318		100	82	
r 319		100	100	
r 320		100	100	
r 321		100	100	

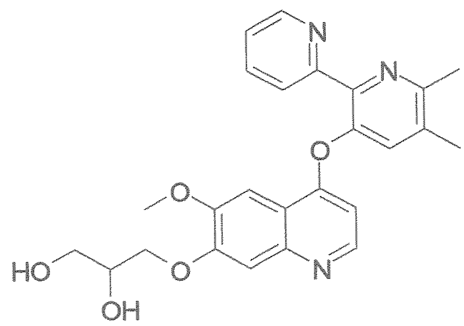
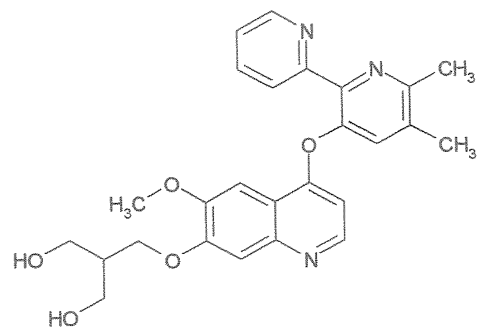
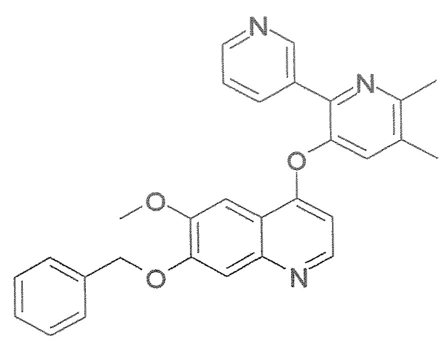
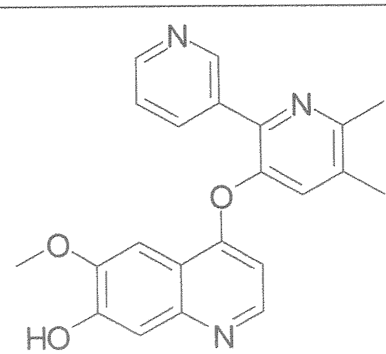
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 322		88	50	
r 323		100	89	
r 324		100	86	
r 325		60	19	

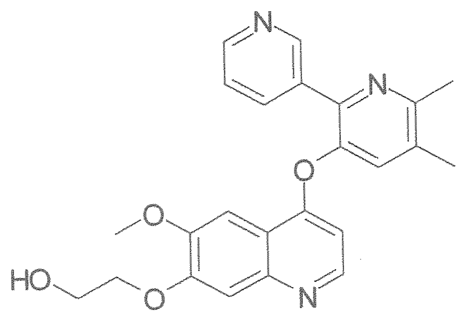
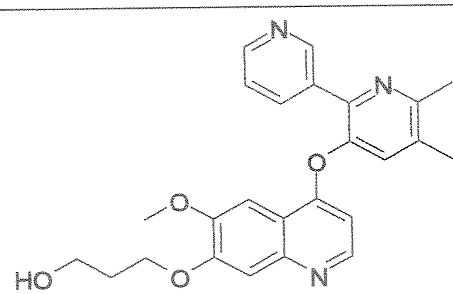
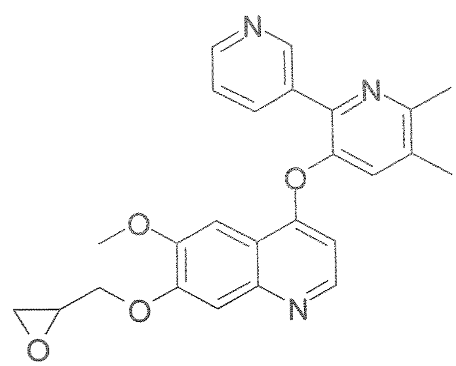
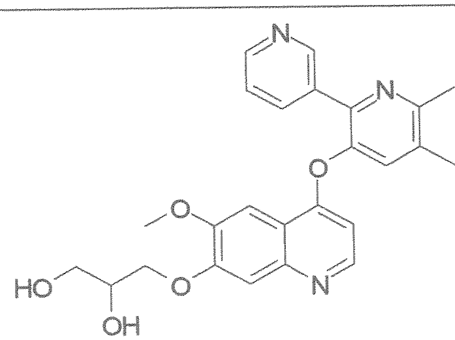
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 326		100	83	
r 327		100	89	
r 328		100	100	
r 329		100	100	

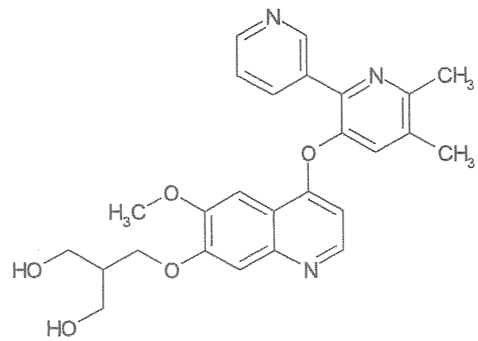
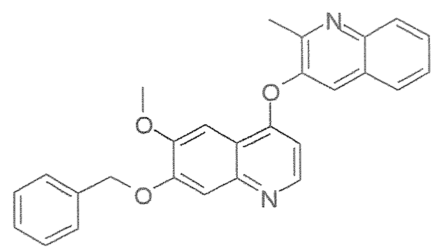
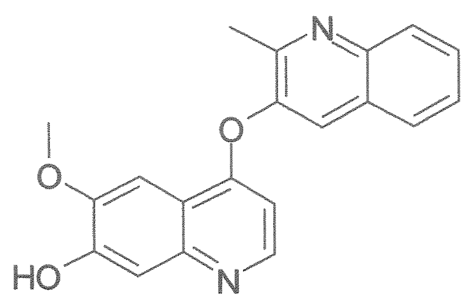
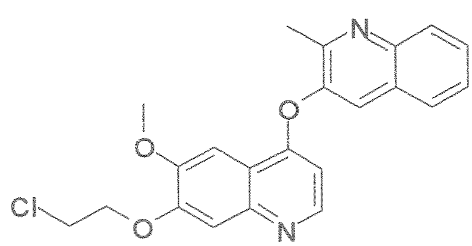
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 330		100	100	
r 331		90	73	
r 332		100	97	
r 333			100	

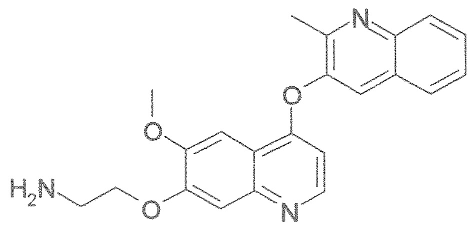
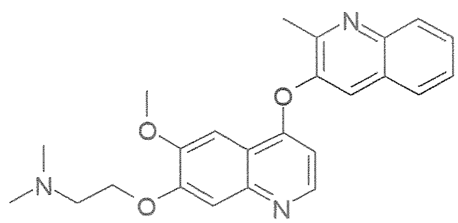
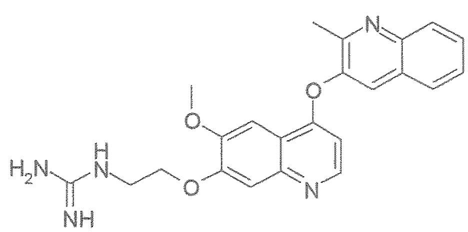
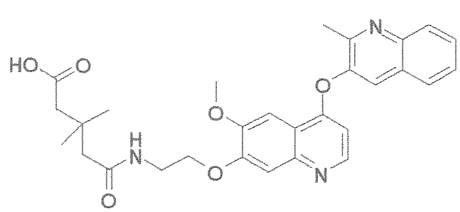
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 334			99	
r 335			100	
r 336			100	
r 337			98	

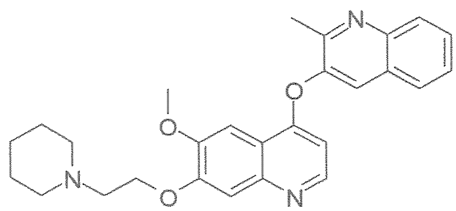
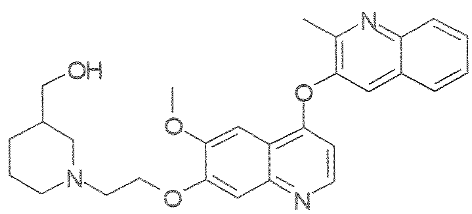
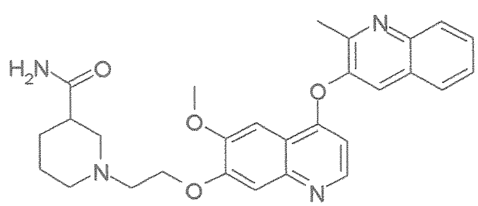
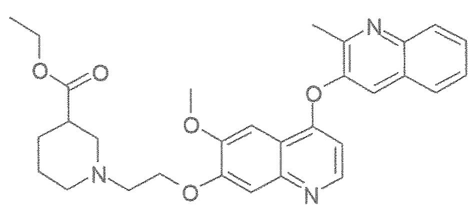
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 338		100	92	
r 339			100	
r 340			99	
r 341			99	

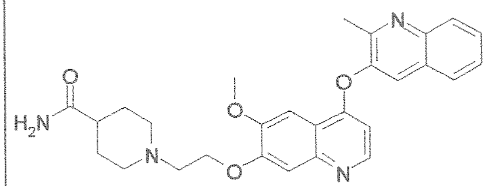
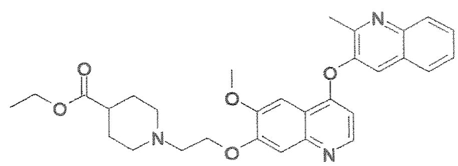
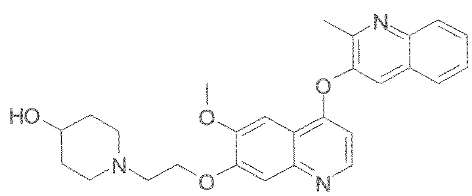
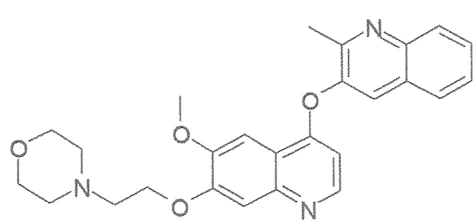
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 342			89	
r 343			93	
r 344			92	
r 345		93	61	

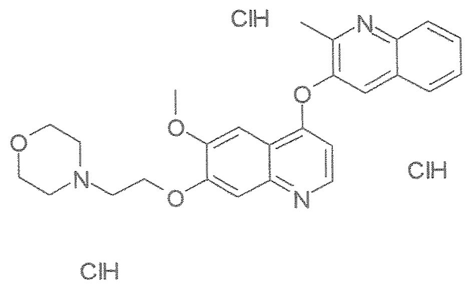
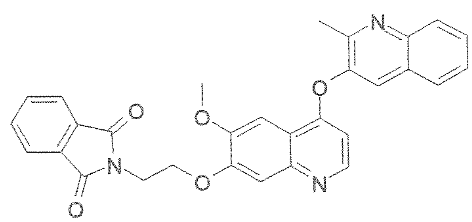
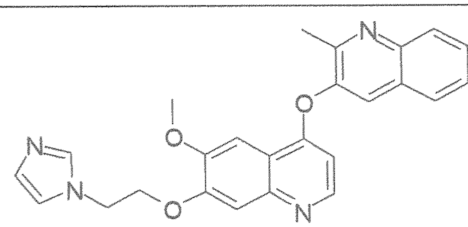
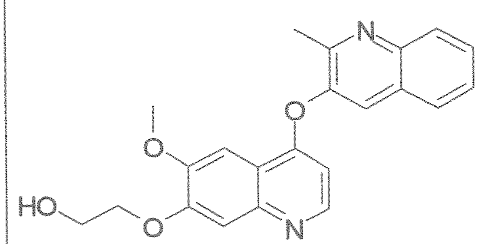
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 346			99	
r 347			100	
r 348			76	
r 349			96	

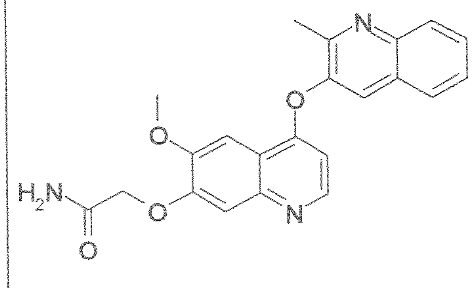
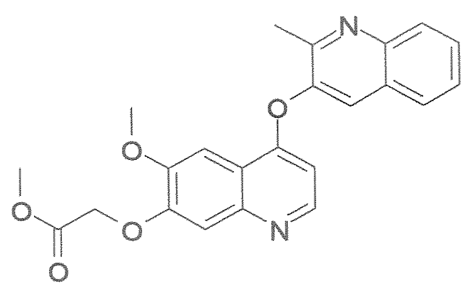
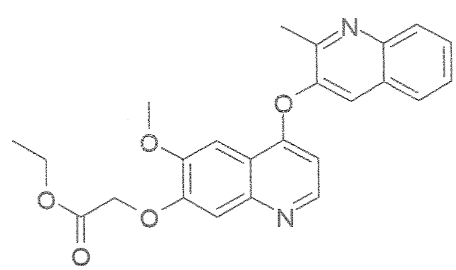
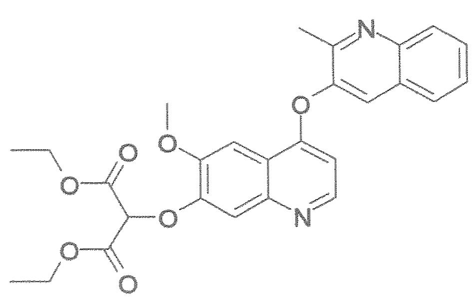
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 350			96	
r 351		90	42	
r 352		68	14	
r 353		86	54	

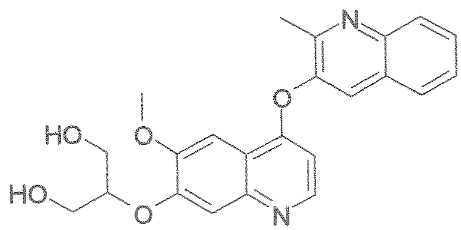
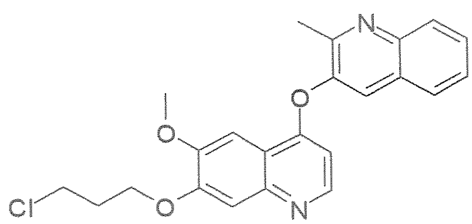
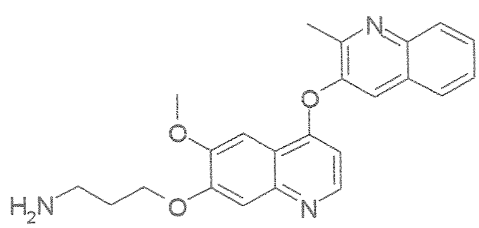
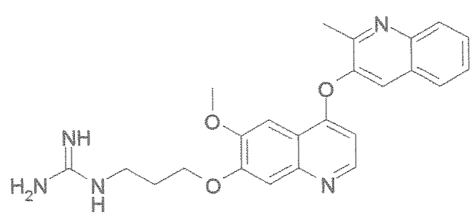
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 354		100	100	
r 355		100	100	
r 356		54	-2	
r 357		60	27	

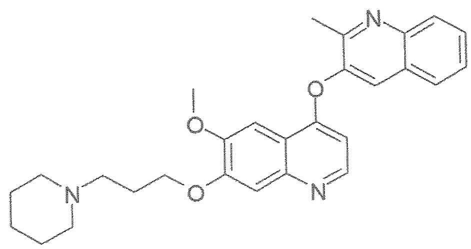
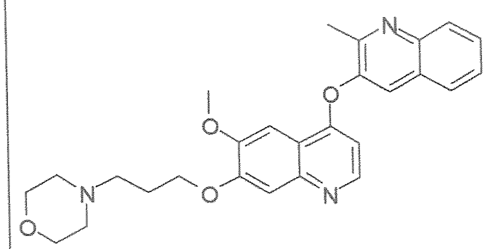
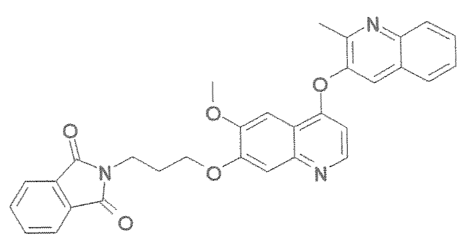
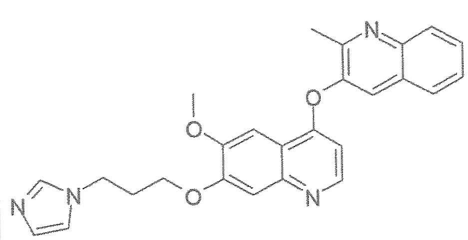
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 358		100	100	
r 359		100	100	
r 360		100	100	
r 361		100	96	

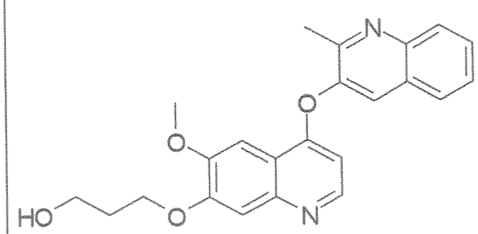
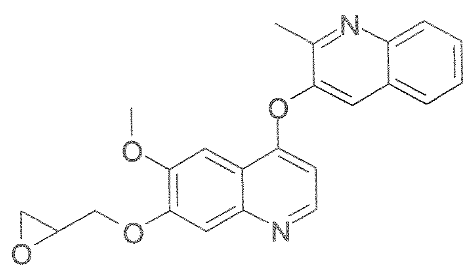
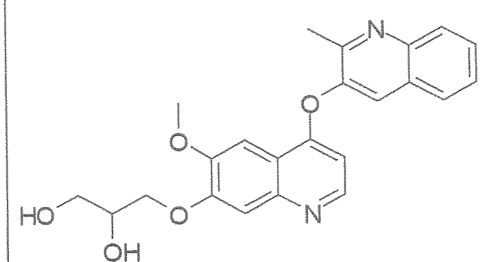
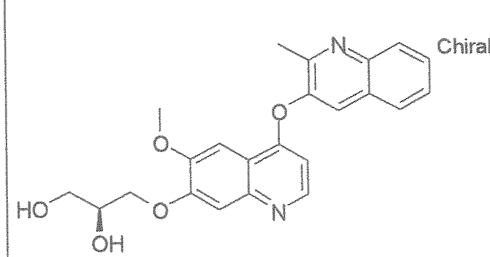
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 362		100	100	
r 363		100	100	
r 364		100	100	
r 365		100	100	

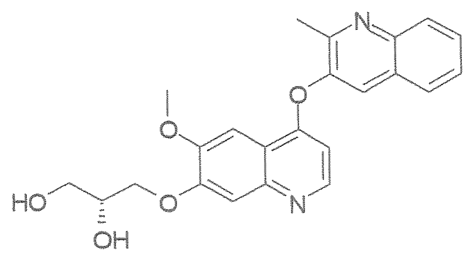
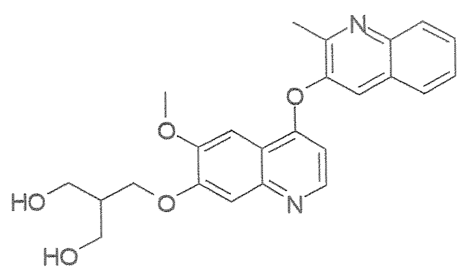
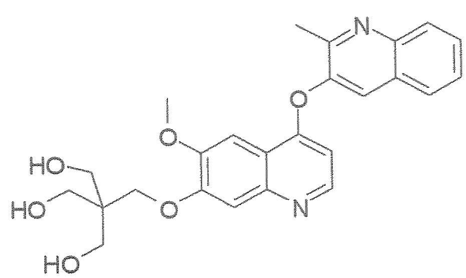
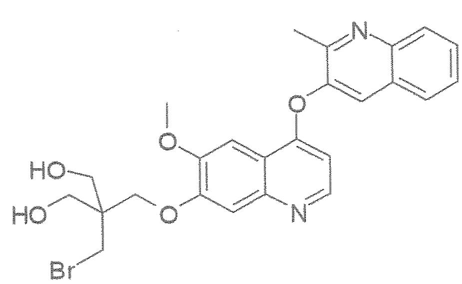
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 366		100	100	
r 367		98	95	
r 368		100	100	
r 369		100	99	

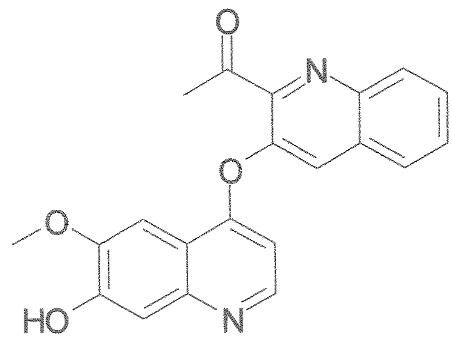
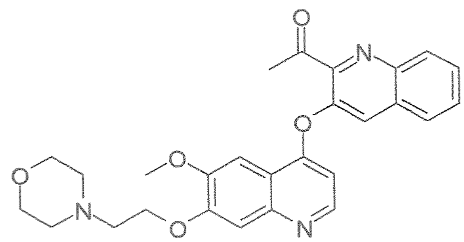
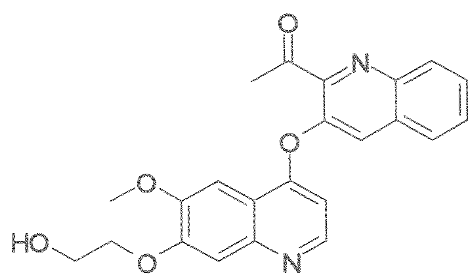
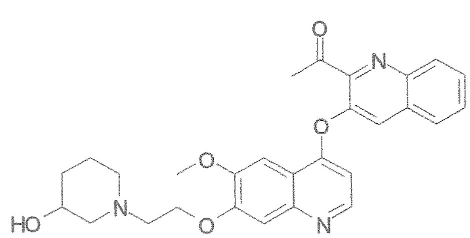
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 370		99	85	
r 371		90	28	
r 372		93	14	
r 373		86	48	

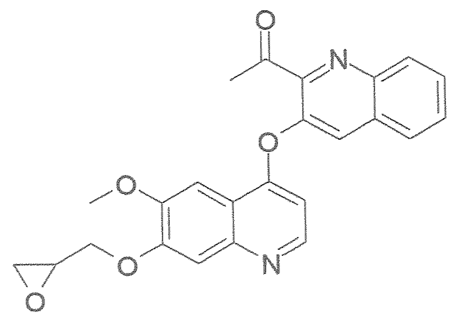
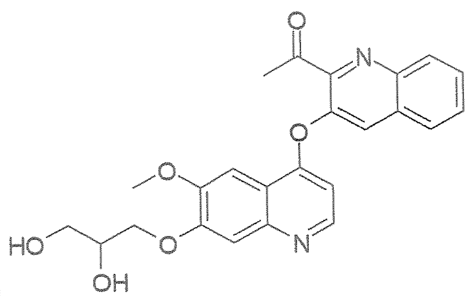
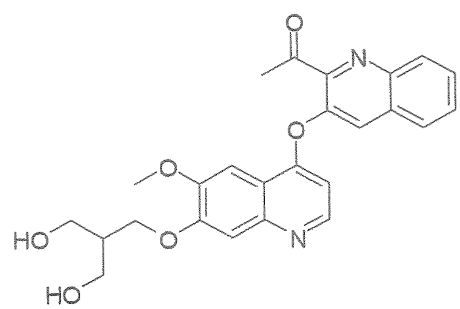
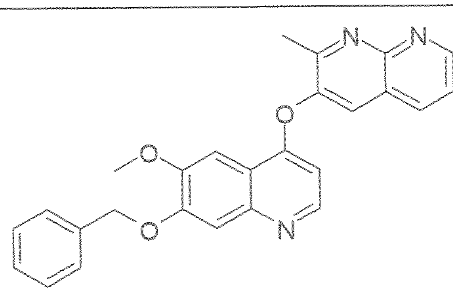
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 374		79	26	
r 375		100	84	
r 376		100	100	
r 377		100	93	

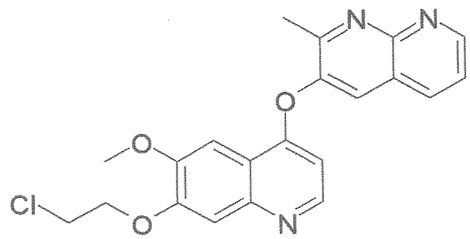
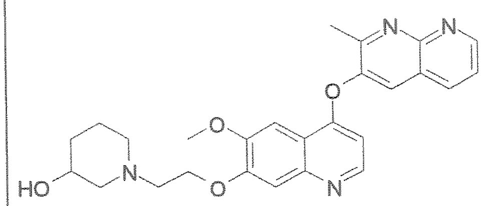
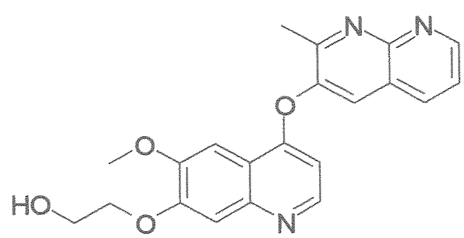
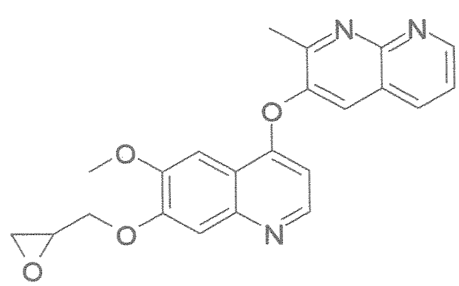
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 378		100	100	
r 379		100	100	
r 380		89	50	
r 381		100	100	

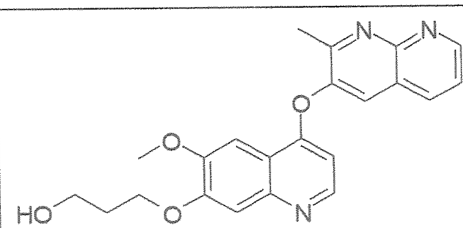
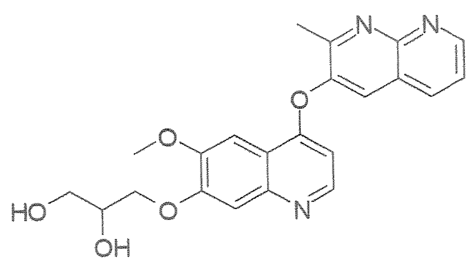
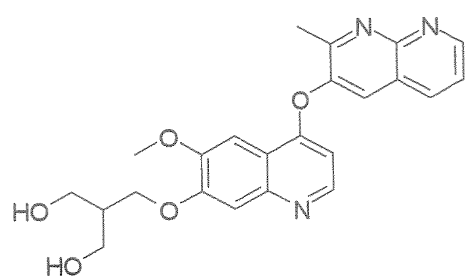
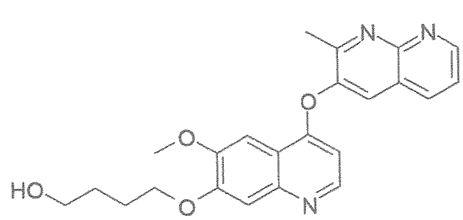
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 382		100	100	
r 383		100	97	
r 384		100	100	
r 385		100	100	

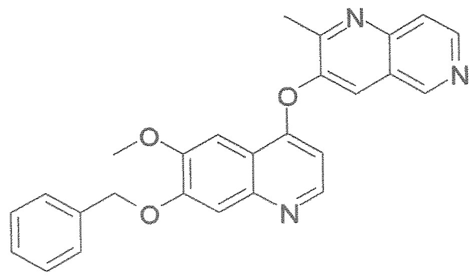
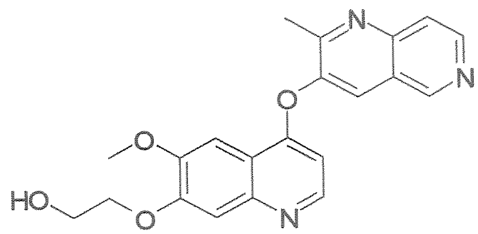
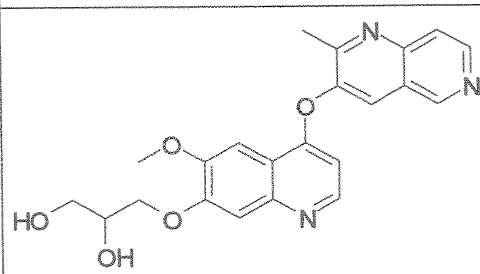
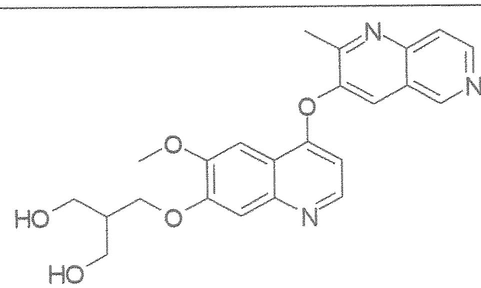
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 386			99	
r 387		100	99	
r 388		100	88	
r 389		100	100	

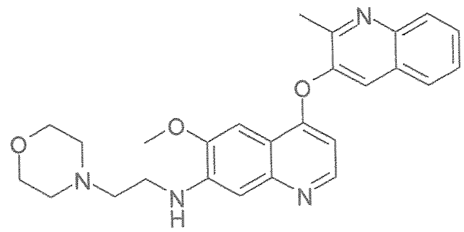
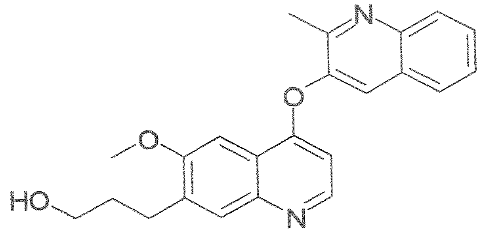
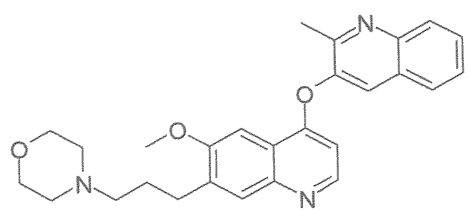
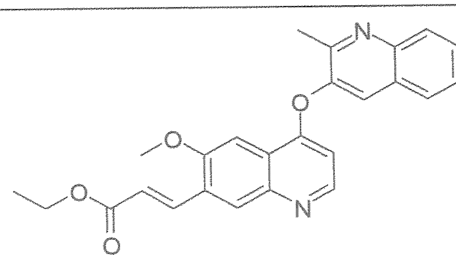
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 390		64	16	
r 391		100	99	
r 392		100	93	
r 393			100	

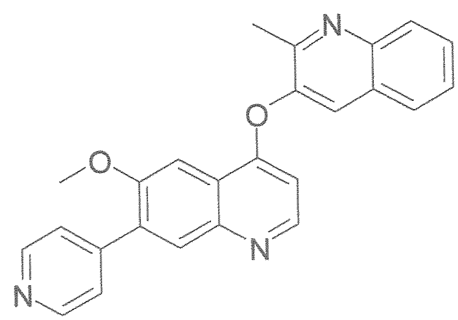
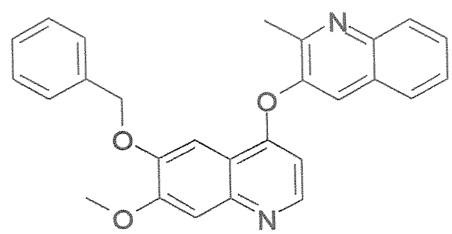
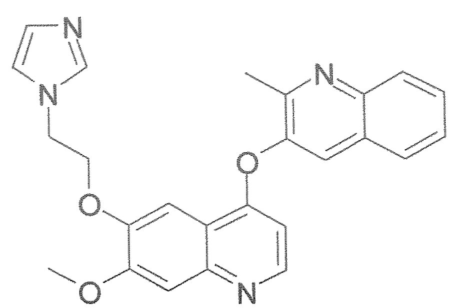
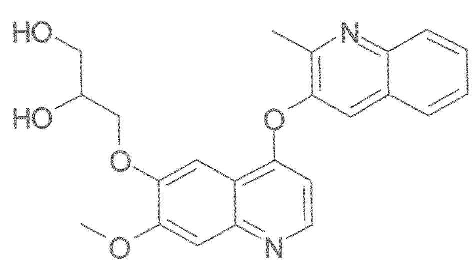
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 394		100	83	
r 395		100	96	
r 396			96	
r 397		100	71	

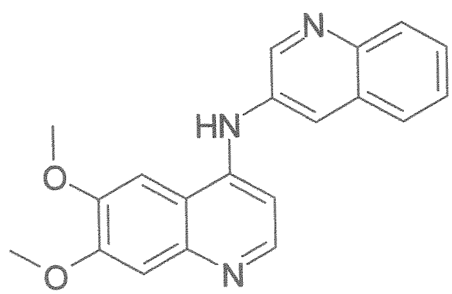
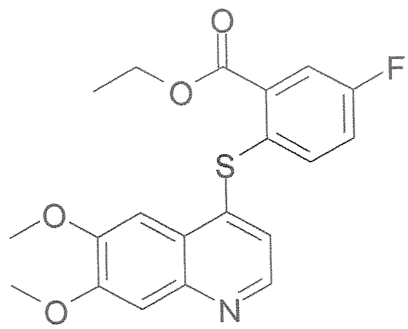
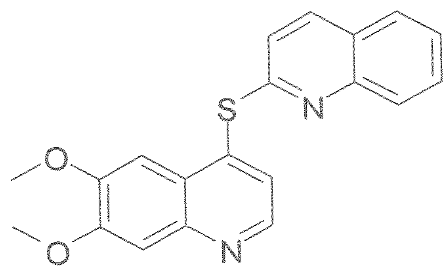
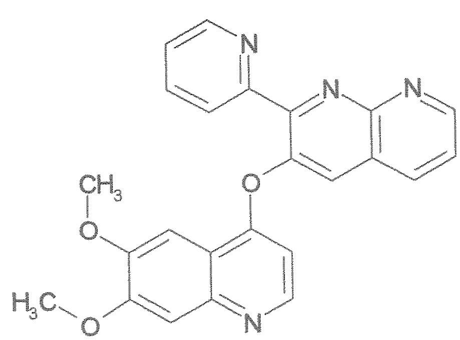
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 398		97	78	
r 399		100	99	
r 400		100	82	
r 401		76	24	

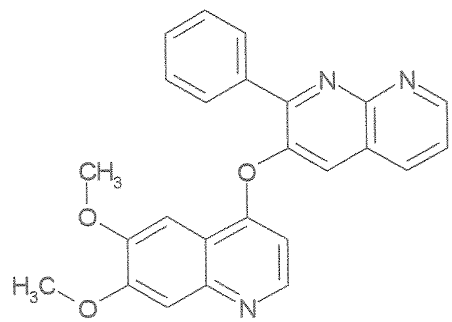
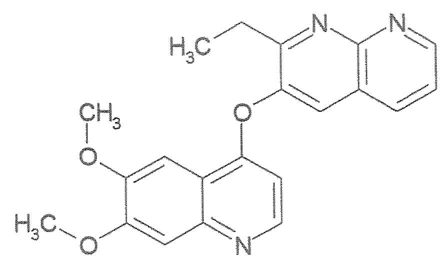
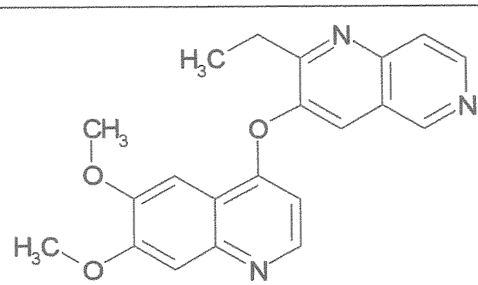
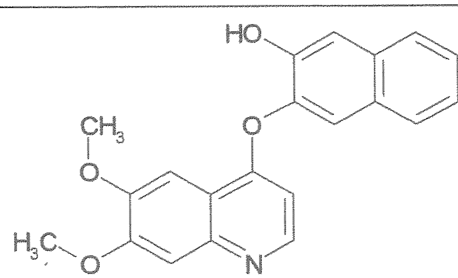
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 402		100	90	
r 403		66	27	
r 404		72	29	
r 405		100	92	

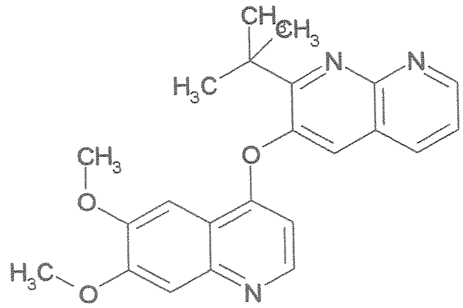
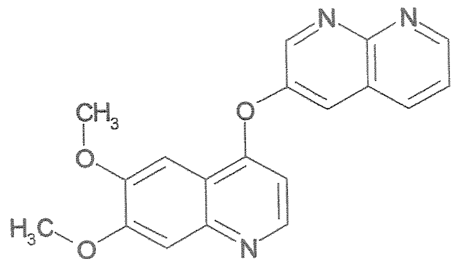
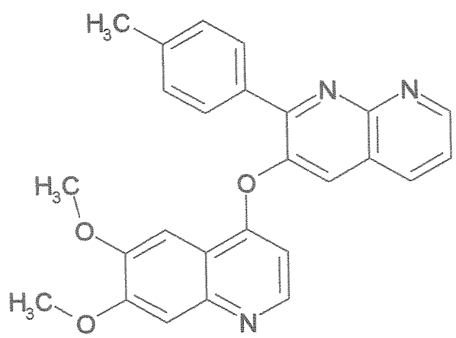
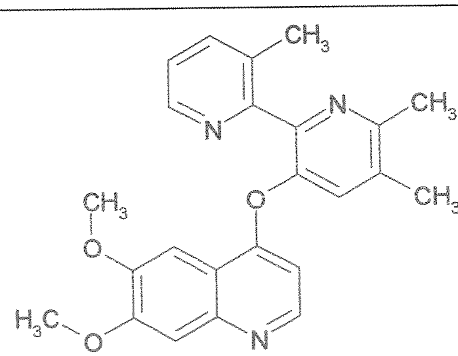
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 406		96	56	
r 407		97	71	
r 408		79	38	
r 409		88	41	

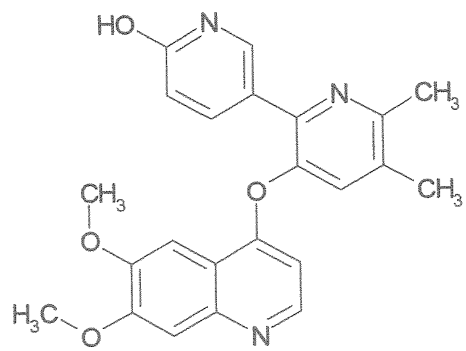
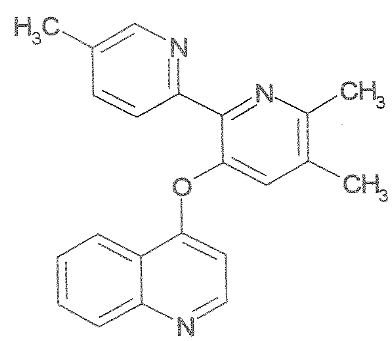
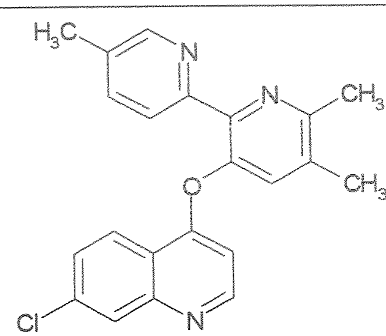
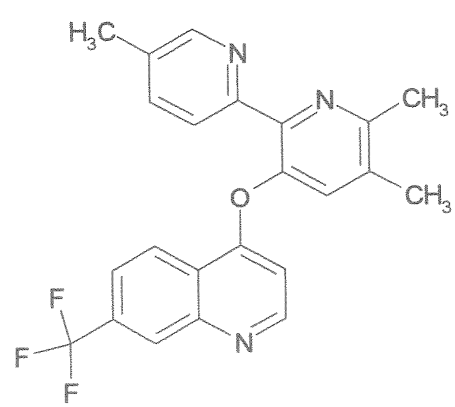
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 410		100	91	
r 411		85	50	
r 412		99	77	
r 413		76	31	

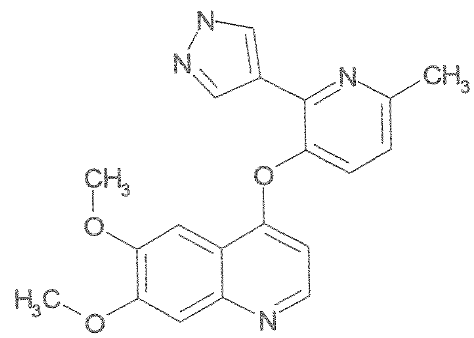
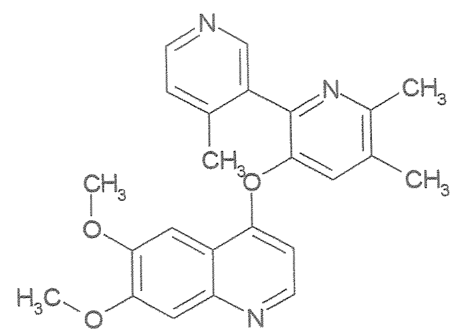
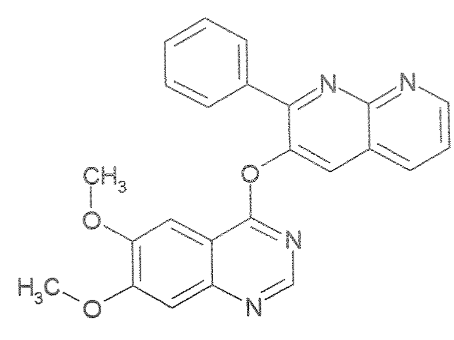
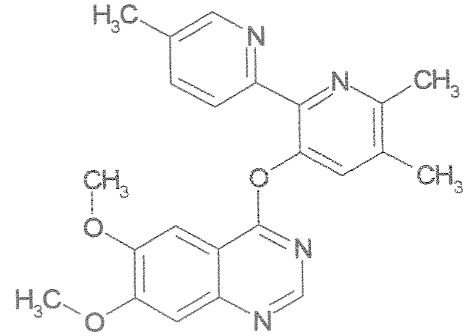
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 414		100	82	
r 415		100	77	
r 416		100	92	
r 417		100	98	

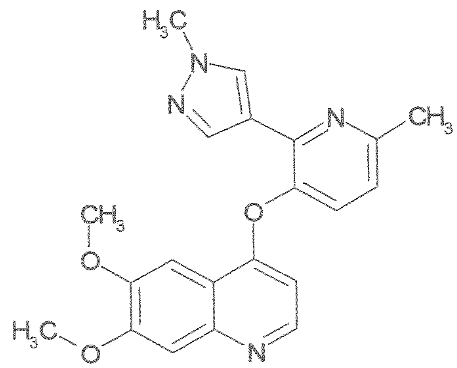
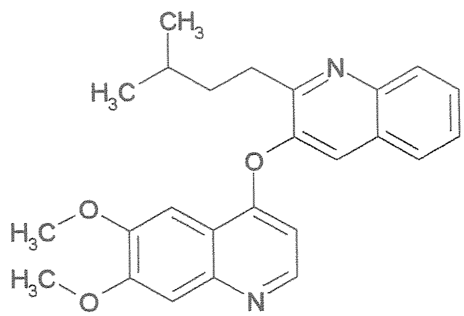
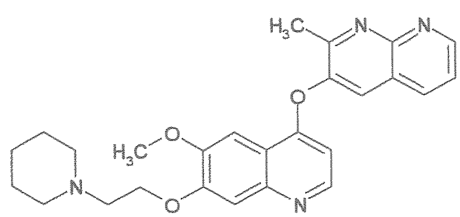
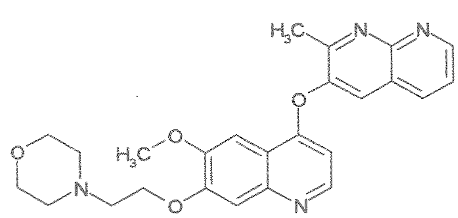
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 418		73	46	
r 419		67	7	
r 420		62	2	
r 421		100	94	

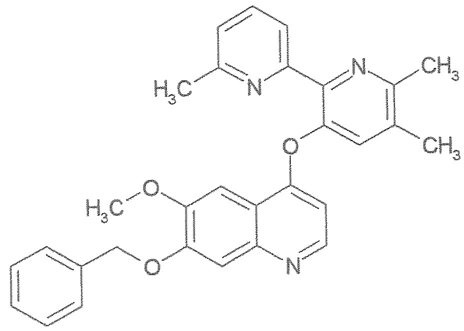
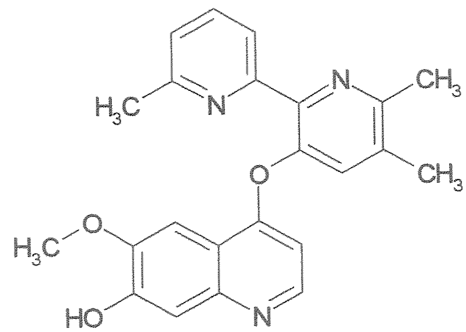
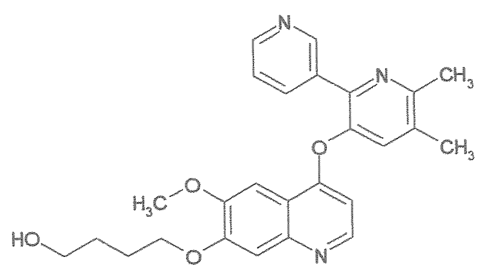
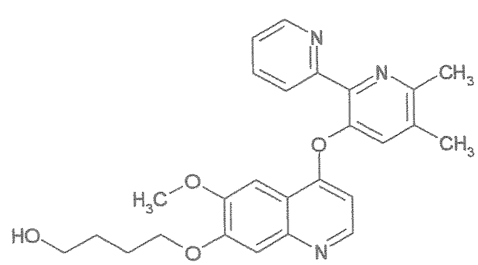
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 422		100	100	
r 423		100	88	
r 424		79	28	
r 425		100	72	

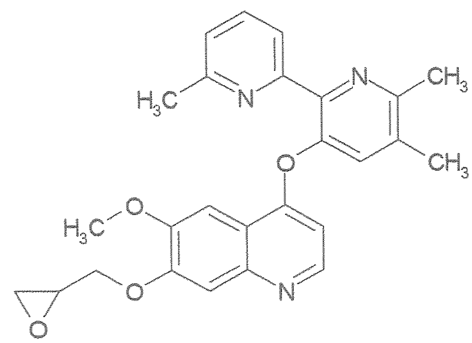
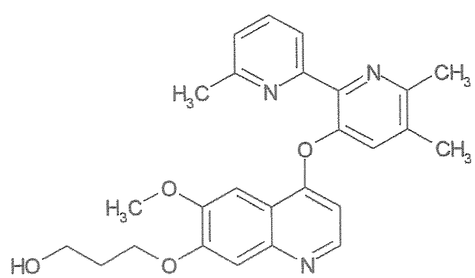
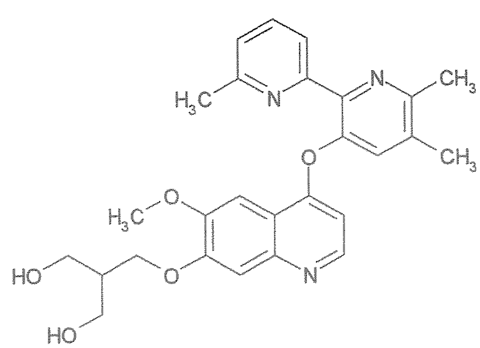
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 426			100	
r 427		80	44	
r 428			67	
r 429		94	52	

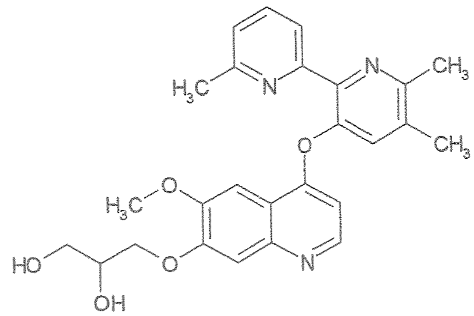
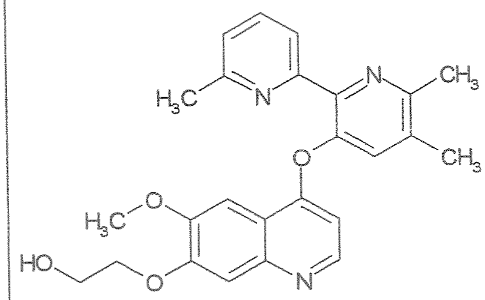
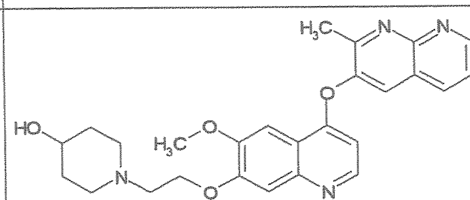
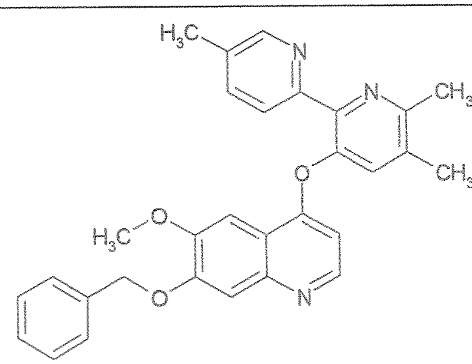
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 430		78	19	
r 431		99	97	
r 432		100	99	
r 433		100	91	

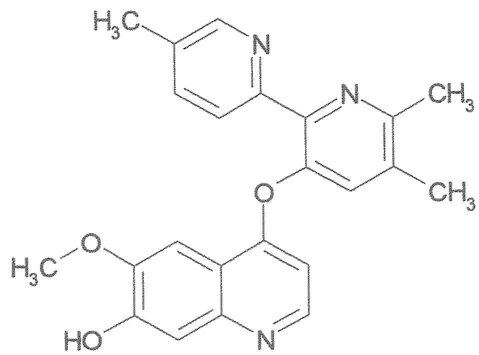
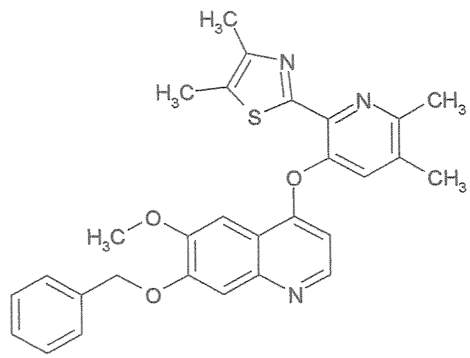
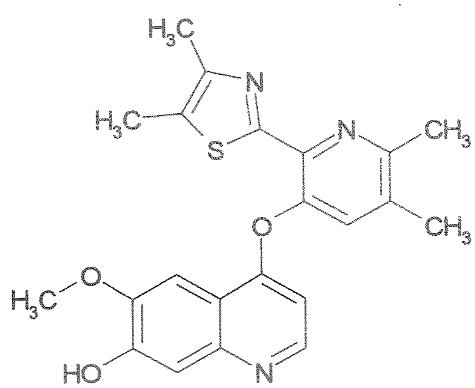
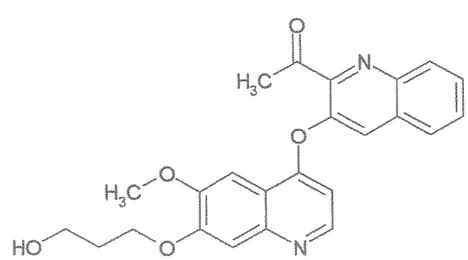
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 434		100	100	
r 435		79	29	
r 436		100	99	
r 437		100	95	

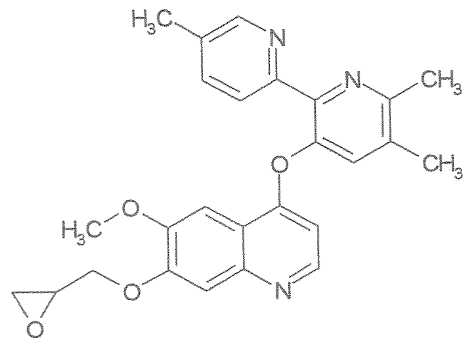
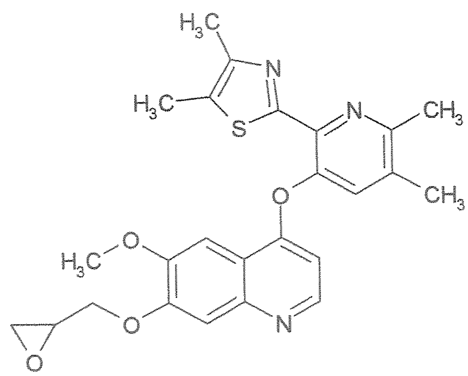
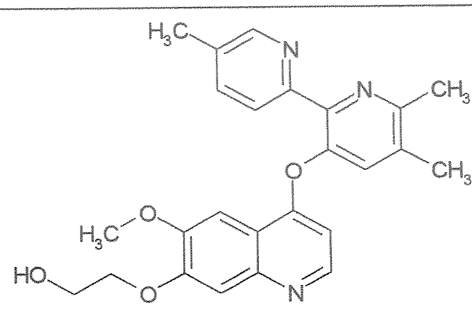
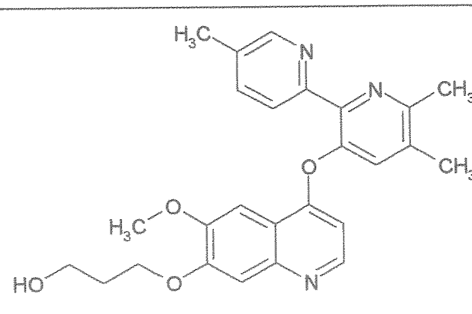
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 438		100	99	
r 439		95	43	
r 440		100	100	
r 441		100	97	

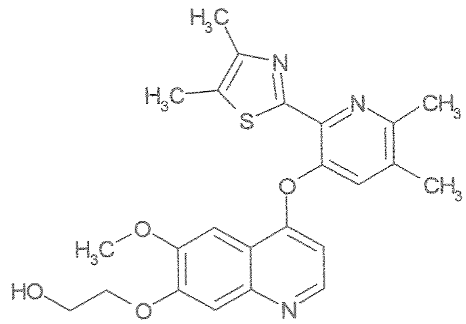
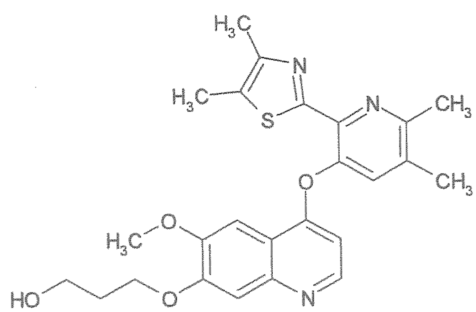
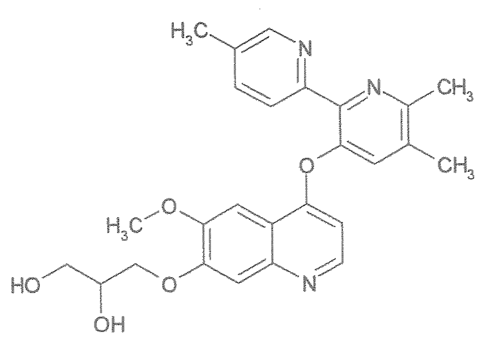
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 442		100	70	
r 443		97	60	
r 444			100	
r 445			99	

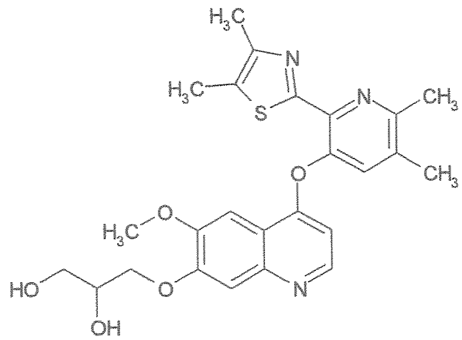
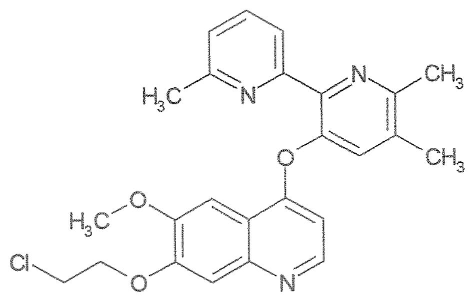
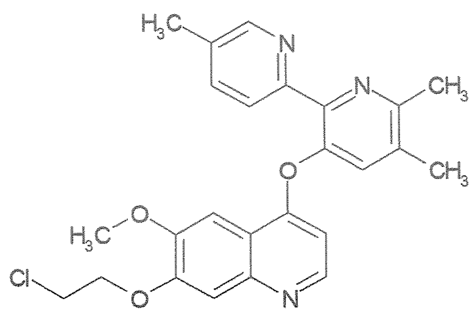
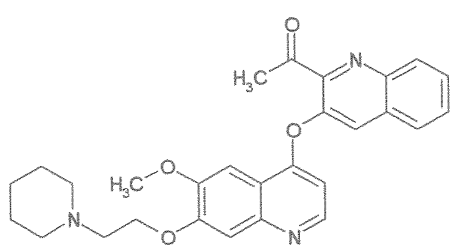
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 446		89	35	
r 447		100	94	
r 448		97	70	

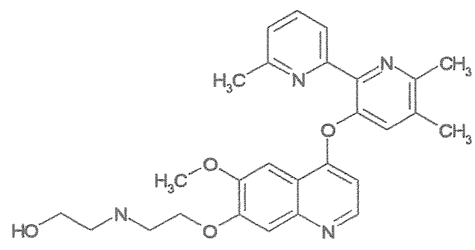
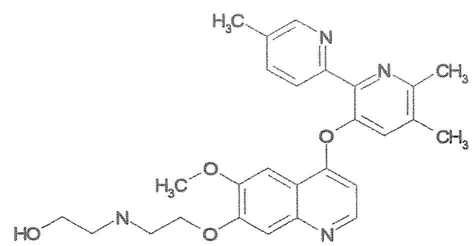
Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 449		98	74	
r 450		100	94	
r 451		100	99	
r 452		99	67	

Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 453		98	72	
r 454		75	41	
r 455		99	76	
r 456		100	99	

Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 457		100	97	
r 458		100	94	
r 459			98	
r 460			97	

Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 461			82	
r 462			99	
r 463		99	77	

Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 464		100	97	
r 465		100	98	
r 466		100	99	
r 467			100	

Compound	Molecular structure	TGFβ inhibition rate, %		
		10 μM	3 μM	1 μM
r 468			99	
r 469			100	

[0541] <u>Test Example 2: Measurement of anti-fibrotic activity using mouse unilateral ureteral obstruction (UUO) model</u>

The anti-fibrotic activity of the compounds related to the present invention was evaluated using a mouse unilateral ureteral obstruction (UUO) model which is a renal fibrosis model. Compound r384 produced in the working example was used as the test compound.

Seven week-old male BALB/c mice (available from Charles River Japan, Inc.) were purchased and were pre-raised before use in experiments. Regarding diets and drinking water, pellets CE-2 (available from CLEA JAPAN INC.) and sterile tap water were freely fed.

The mice underwent laparotomy under pentobarbital anesthesia, and the left renal urinary duct was ligated. Thereafter, the mice underwent suturing operation and were divided into a vehicle administration group (n = 7) and a

test compound administration group (n = 7) using the weight as an index.

The test compound was weighed, and then one drop of 1 N HCl was added to the test compound to prepare a solution. The solution was then suspended in 0.5% carboxymethylcellulose (solvent). The suspension was forcibly orally administered twice a day with an oral sonde from the day of urinary duct ligation (5, 15, or 50 mg/kg). The solvent was administered to the vehicle administration group in the same manner as described just above.

[0542] After administration for 4 days, the mouse left kidney was removed, and the hydroxyproline content as an index of organ fibrosis was measured by the following method.

Renal pieces were first placed in 6 N HCl, were homogenized, and were then heated on a heat block at 130°C for 3 hr to hydrolyze protein. Thereafter, the suspension of renal pieces was neutralized by the addition of an appropriate amount of 4 N NaOH. The neutralized suspension was centrifuged (1000 rpm, 5 min, room temperature) to obtain the supernatant as a kidney extract. A chloramine T liquid, a perchloric acid solution (a solution prepared by adding distilled water to 31.5 ml of 60% perchloric acid to adjust the total volume to 100 ml), and a p-dimethylaminobenzaldehyde solution (a solution prepared by adding methylcellulose to 20 g of p-dimethylaminobenzaldehyde to adjust the total volume to 100 ml) were added to the kidney extract, and the reaction was allowed to proceed at 60°C for 20 min. The absorbance at 557 nM was then measured. The content of hydroxyproline was determined from the measured data based on a calibration curve for hydroxyproline prepared using control. Further, the content of hydroxyproline thus determined was corrected according to the weight of the homogenized kidney.

[0543] The results were as shown in Table 2. The values in the table are average of data on 7 mice for each group ± standard deviation.

The result showed that the content of

hydroxyproline in the UUO treatment mouse kidney was increased as compared with the kidney of normal mice, suggesting that extracellular matrix proteins were accumulated within the kidney. In contrast, the content of hydroxyproline in the mouse to which the test compound had been administrated was lowered, as compared with that of the solvent administration group, indicating that the compound could suppress the accumulation of extracellular matrix proteins in the kidney.

[0544] Table 2:

Administration group	Hydroxyproline content (mg/g)
Normal mice	392.9 ± 10.8
UUO treatment + solvent	549.4 ± 15.2 ###
UUO treatment + compound r384 (5 mg/kg)	514.4 ± 20.8
UUO treatment + compound r384 (15 mg/kg)	487.7 ± 10.9 **
UUO treatment + compound r384 (50 mg/kg)	425.7 ± 14.2 ***

In the table, ### indicates that $p < 0.001$ in Student's t-test against the normal mouse group, and ** and *** respectively indicate that $p < 0.01$ and $p < 0.001$ in Student's t-test against UUO treatment + solvent group.

[0545] Test Example 3: Measurement of anti-fibrotic activity using mouse unilateral ureteral obstruction (UUO) model

The anti-fibrotic activity of a compound related to the present invention was evaluated using the same model as used in Test Example 2.

Compound r320 prepared in the working example was used as the test compound.

The experiment method and evaluation method were the same as those in Test Example 2, except that the

compound administration was carried out by feeding a diet mixed with the compound for 10 days and the correction of hydroxyproline content was changed to the content of protein in the kidney extract.

The results were as shown in Table 3. The values in the table are average of data on five mice for each group ± standard deviation.

The result showed that the content of hydroxyproline in the UUO treatment mouse kidney was increased as compared with the kidney of normal mice, suggesting that extracellular matorix was accumulated within the kidney. In contrast, the content of hydroxyproline in the mouse to which the test compound had been administrated was lowered, as compared with that of the solvent administration group, indicating that the compound could suppress the accumulation of extracellular substrate in the kidney.

[0546] Table 3:

Administration group	Hydroxyproline content (mg/g protein)
Normal mice	6.7 ± 1.26
UUO treatment + solvent	12.7 ± 1.14 #
UUO treatment + compound r320 (0.1% mixed feed)	9.44 ± 0.53 *
UUO treatment + compound r320 (0.3% mixed feed)	9.19 ± 0.38 *

In the table, # indicates that $p < 0.05$ in Student's t-test against the normal mouse group, and ** indicates that $p < 0.05$ in Student's t-test against UUO treatment + solvent group.

[0547] Test Example 4: Measurement of anti-fibrotic activity using mouse DMN hepatic fibrosis model

The anti-fibrotic activity of a compound related to the present invention was evaluated using a mouse DMN hepatic fibrosis model as a liver fibrosis model. Compound r384

prepared in the working example was used as the test compound.

Six-week-old male BALB/c mice (available from Charles River Japan, Inc.) were purchased and were pre-raised before use in experiments.

The mice were divided into a vehicle administration group (n = 6) and a test compound administration group (n = 7) using the weight as an index. Thereafter, dimethylnitrosoamine (DMN) diluted with physiological saline was intraperitoneally administered at 15 mg/kg three times per week for 3 weeks to induce hepatic fibrosis.

The administration of the test compound was carried out from the first day of the DMN administration. The test compound was mixed at the dosage of 0.015, 0.03, and 0.06% in powder diet CE-2 (available from CLEA JAPAN INC.), and the mixtures were fed as a diet to each mouse group.

After 21 days, the mice underwent laparotomy under ether anesthesia, and blood was collected from the heart, followed by measurement of the level of hyaluronic acid in blood as an index of hepatic fibrosis using a hyaluronic acid plate (Chugai Pharmaceutical Co., Ltd.).

[0548] The results were as shown in Table 4. The values in the table are average of data on 6 mice for each group ± standard deviation.

The result showed that the blood hyaluronic acid level in the mouse liver to which DMN had been administered was increased as compared with the liver of normal mice, suggesting that extracellular matrix proteins were accumulated within the liver. In contrast, the blood hyaluronic acid level in the mouse to which the test compound had been administered was lowered as compared with that of the solvent administration group, indicating that the compound could suppress the accumulation of extracellular matrix proteins in the liver.

[0549] <u>Table 4:</u>

Adminstration group	Blood hyaluronic acid content (ng/ml)
Normal mice	113.8 ± 14.9
DMN administration + solvent	326.4 ± 47.1 ##
DMN administration + compound r384 (0.015% mixed feed)	167.8 ± 25.0 *
DMN administration + compound r384 (0.03% mixed feed)	108.5 ± 9.0 **
DMN administration + compound r384(0.06% mixed feed)	97.2 ± 11.0 **

In the table, ## indicates that $p < 0.01$ in Student's t-test against the normal mouse group, and * and ** respectively indicate that $p < 0.05$ and $p < 0.01$ in Student's t-test against UUO treatment + solvent group.

[0550] <u>Test Example 5: Measurement of anti-fibrotic activity using rat unilateral ureteral obstruction (UUO) model</u>

The anti-fibrotic activity of the compounds described in the present specification was evaluated using a rat unilateral ureteral obstruction (UUO) model which is a renal fibrosis model. Compound 50 and compound 159 were used as the test compound.

Six week-old male SD rats (available from Charles River Japan, Inc.) were purchased and were pre-raised before use in experiments. Regarding diets and drinking water, pellets CE-2 (available from CLEA JAPAN INC.) and sterile tap water were freely fed.

The rats underwent laparotomy under pentobarbital anesthesia, and the left renal urinary duct was ligated. Thereafter, the mice underwent suturing operation and were divided into a vehicle administration group (n = 6) and a test compound administration group (n = 6) using the weight as an index.

The test compound was mixed in amounts of 0.03%

and 0.1% in powder diet CE-2 (available from CLEA JAPAN INC.), and the mixtures were fed as a diet to each rat group from the first day of the ureteral obstruction.

[0551] After administration of the mixed feed for 7 days, the left kidney was removed, and the hydroxyproline content as an index of organ fibrosis was measured by the following method. Specifically, renal pieces were first placed in 6 N HCl, were homogenized, and were then heated on a heat block at 130°C for 3 hr to hydrolyze protein. Thereafter, the suspension of renal pieces was neutralized by the addition of an appropriate amount of 4 N NaOH. The neutralized suspension was centrifuged (1000 rpm, 5 min, room temperature) to obtain the supernatant as a kidney extract. A chloramine T liquid, a perchloric acid solution (a solution prepared by adding distilled water to 31.5 ml of 60% perchloric acid to adjust the total volume to 100 ml), and a p-dimethylaminobenzaldehyde solution (a solution prepared by adding methylcellulose to 20 g of p-dimethylaminobenzaldehyde to adjust the total volume to 100 ml) were added to the kidney extract, and a reaction was allowed to proceed at 60°C for 20 min. The absorbance at 557 nM was then measured. The content of hydroxyproline was determined from the measured data based on a calibration curve for hydroxyproline prepared using control. Further, the content of hydroxyproline thus determined was corrected according to the total protein content of the kidney extract.

[0552] The results were as shown in Tables 5a and 5b.

The values in the tables are average of data on 6 rats for each group ± standard deviation. The result showed that the content of hydroxyproline in the UUO treatment rat kidney was increased, as compared with the kidney of normal rats, suggesting that extracellular matrix proteins were accumulated within the kidney. In contrast, the content of hydroxyproline in the rat administrated the test compounds was lowered as compared with the solvent administration group, for the group to which had been administered, , indicating that the compounds could suppress the accumulation of extracellular

matrix proteins in the kidney.

[0553] Table 5a:

Administration group	Hydroxyproline content (mg/g)
Normal rats	4.47 ± 0.17
UUO treatment + solvent	8.24 ± 0.31 ###
UUO treatment + compound 50 (0.03% mixed feed)	7.33 ± 0.67
UUO treatment + compound 50 (0.1% mixed feed)	4.67 ± 0.22 ***

[0554] Table 5b:

Administration group	Hydroxyproline content (mg/g)
Normal rats	18.84 ± 1.05
UUO treatment + solvent	27.16 ± 2.65 ###
UUO treatment + compound 159 (0.03% mixed feed)	22.47 ± 0.82
UUO treatment + compound 159 (0.1% mixed feed)	17.28 ± 0.87 ***

In the tables, ### indicates that $p < 0.001$ in Student's t-test against the normal rat group, and *** indicates that $p < 0.001$ in Student's t-test against UUO treatment + solvent group.

[0555] Test Example 6: Measurement of cell growth inhibitory activity using A549 cells

Human lung cancer epithelial cells (A549) (available from ATCC) were suspended to a concentration of 3×10^4/ml in a DMEM/F12 medium containing 10%FCS, and the suspension was inoculated in 100 μl portions in wells of a 96-well plate.

On the following day, a stock solution of the test compound which had been adjusted to 10 mM with DMSO was adjusted with a serum-free DMEM/F12 medium to a dose (60 μM) which was twice the evaluation concentration. After

removing the medium inoculated in the 96 wells on the previous day, the solution was added in 50 μl portions to the plate. Next, a DMEM/F12 medium containing 10% serum was added in 50 μl portions to the wells, followed by culturing at 37°C for 40 hr.

The final concentration of the serum and the concentration of the evaluation compound were 5% and 30 μM, respectively. The compounds according to the present invention synthesized in the working example were used as the test compound. Compounds 261, 269 and 274 described in WO 2004/018430 were used as the comparative compound.

[0556] After 40 hr, the culture was removed, and 100 μl of a solution prepared by diluting counting kit-8 (purchased from Dojindo) with a serum-free F12 medium by 10 times was added, followed by culturing at 37°C for 20 to 30 min. After the confirmation of suitable color development, the absorbance at 450 nM was measured with ARVO (purchased from Wallach Bethold Japan). The cell growth inhibition in the test compound added wells were determined by presuming the absorbance value in the test compound-free wells to be 0% and the absorbance value in the cell-free wells to be 100%.

[0557] The results were as shown in Table 6. As is apparent from Table 6, the conventional compounds had a cell growth inhibition of about 30% to 45%, whereas the test compounds had substantially no cell growth inhibitory activity, indicating that the test compounds had a significantly improved potential as a medicament.

[0558] Table 6:

Test compound	Cell growth inhibition rate (%)
Compound 261 of WO 2004/018430	44
Compound 269 of WO 2004/018430	45
Compound 205	9
Compound 179	-3
Compound 181	-7
Compound 182	-8

Compound 184	8
Compound 186	-2
Compound 187	0
Compound 274 of WO 2004/018430	25
Compound 192	3
Compound 194	-15
Compound 200	0
Compound 201	2
Compound 202	8
Compound 204	-9
Compound 206	-1
Compound 217	4
Compound 222	6
Compound 225	8

[0559] Test Example 7: Measurement of BMP signal inhibitory activity (in-vitro test)

The inhibitory activity of the compounds according to the present invention against BMP signals was studied using a cell line through which TGFb and BMP signals can be simultaneously observed.

Specifically, the cell lines capable of detecting the two signal was generated by transfecting reporter plasmids for detection of TGFb and BMP signals into a human hepatocarcinoma cell line HepG2(available from ATCC) and was used as evaluation cells. For detection of TGF-beta signal, the plasmid having four tandem binding sequences of Smad2/3, TGF-beta signal transducers, to the upstream of a luciferases gene were used as a reporter plasmid (p(SBE)4-Luc/hygro). For detection of BMP signal, the plasmid having twelve tandem binding sequences of Smad1/5/8, BMP signal transducers, to the upstream of a luciferases gene were used as a reporter plasmid (p(GCCG)12-Luc/neo), according to the method described in Mol Biol Cell. 2000 11(2): 555-65.

The test compound and TGFβ-1 (2 ng/ml) or BMP4 (20 ng/ml) were added to the cells, and the mixture was

cultured for 4 hr. The compounds according to the present invention synthesized in the working example were used as the test compound. Compounds 261, 269 and 274 described in WO 2004/018430 were used as the comparative compound. After the culture, the luciferase activity of the cells was measured by chemiluminescence (Steady Glo (trademark) luciferase assay system, available from Promega).

Likewise, the luciferase activity was measured as control for the culture of cells with only TGFβ or BMP4 added thereto and the culture of cells with the addition of none of TGFβ, BMP4 and the test compound.

The inhibitory activity IC50 of the compounds against TGFβ and BMP4 was calculated based on the results of measurement, and the kinase selectivity for BMP4 was determined by the following method.

Kinase selectivity for BMP4 (times) = Inhibitory activity against BMP4 signal (IC50)/Inhibitory activity against TGFβ signal (IC50)

[0560] The results were as shown in Table 7.

As is apparent from the table, the selectivity of the conventional compounds was as low as about four times to ten times, whereas, for all the test compounds, the selectivity for BMP signal was 20 times or higher, indicating that the test compounds had a significantly improved potential as a medicament.

[0561] Table 7:

Test compound	Selectivity for BMP (times)
Compound 261 of WO 2004/018430	4.1
Compound 269 of WO 2004/018430	11.9
Compound 181	308
Compound 182	195
Compound 184	> 428
Compound 187	72
Compound 274 of WO 2004/018430	6.7

Compound 192	> 176
Compound 194	51
Compound 200	75
Compound 202	21.4

[0562] This application is based upon and claims the benefit of priority from the prior Japanese Patent Applications No. 45383/2004, filed on February 20, 2004, the entire contents of which are incorporated herein by reference.